Pharmaceuticals, Corporate Crime and Public Health
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Preface

Organizations, whether they be societies, foundations or commercial corporations, are as a rule brought into existence to put into motion the hopes and ideals of those who create and lead them. At the same time, they justify and finance their existence primarily by providing some form of service to society. To a very large extent, therefore, society has come to rely upon their existence and to encourage their development. That applies to the pharmaceutical industry as it does to others.

On the other hand, the community must remain watchful. Whatever the motives for their creation, these bodies over the years grow, change, merge and alter course; an institution that has served society well at one stage may later fail to do so. Just as in the case of individual citizens, society therefore needs to create rules of behaviour, laid down in the form of laws and regulations, orders and codes, and to ensure compliance with them. In many an instance those rules will closely parallel the standards that a right-minded corporation believes must govern its own acts. In some other matters, however, the community will find it necessary to impose further constraints on a company or an entire industry where a conflict has emerged between certain interests of the body in question and those of society as a whole.

Where medicines are concerned, the community has a very particular interest in ensuring that there is an acceptable balance between the reasonable desire of a producer to seek a fair reward for its efforts and the extent to which its products are capable of fulfilling the hopes and expectations of those who make use of them. Many medicines are life-saving; many more relieve suffering, speed recovery from illness or protect the individual from infection. Just as patients have a right to expect that their doctors, surgeons or pharmacists will at all times act in the best interests of those who rely on them, so too are they surely entitled to believe that those who develop and make medicines will be doing their best to serve the individuals who take them. No doctor is infallible and no medicine is universally effective; in either case, however, it is reasonable to expect a modicum of honest effort, truth and support.
Although views on medicines are diverse, and in some respects fluid or controversial, no one will challenge the major role that they can play in health care, as they have done for centuries. Controversy with respect to medicines has related primarily to the increasingly dominant (and sometimes questionable) role played by commercial interests in their preparation, promotion and sale. By the seventeenth century in Europe and North America a thriving trade in the production and supply of medicines had come into being; two centuries later, major industrial firms were emerging to provide packaged pharmaceuticals. Among the makers of medicines there have been scientific pioneers of the first order, but alongside them one has repeatedly encountered mere charlatans and heartless profiteers. The patient in a sickbed and even the doctor in a consulting room may be poorly placed to distinguish the good from the bad; but progressively the law has come to their aid, setting standards for medicines and taking measures to ensure that these are respected. It is an ongoing story, but one in which there is a constant hope of betterment, particularly as notions of commercial ethics have become better defined, though not always respected.

In the course of the twentieth century, with the emergence of massive industrial corporations in this sector as in others, society has become ever more aware of the manner in which corporate power may be abused and may pose risks for the society that these corporations profess to serve. In 1984 John Braithwaite published Corporate Crime in the Pharmaceutical Industry. Based both on knowledge that at that time was becoming more generally available and upon his examination of the phenomenon in the United States, Australia, Guatemala and Mexico, that book recognized and defined many forms of malpractice that are still all too evident in the sector today. The fact that these challenges to society have within the last generation become more severe, more widespread and sometimes more subtle provides one sound reason for the present volume. It is however also a fact that within that period the entire concept of corporate crime as a social phenomenon has become much more clearly defined. For such reasons this book sets out to complement John Braithwaite’s study of a generation ago; it provides a detailed view of the problem as it exists today.

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now, in the early years of the twenty-first century: appropriately, it culminates in an analysis by John himself of the current scene and his view of the future.

This study is by no means a witch-hunt directed against the pharmaceutical industry. It acknowledges this industry's positive achievements, but it takes a frank look at its less creditable side. Corporations both large and small have repeatedly let down their team, soiled their own reputations and betrayed the trust that society has placed in them. Attempts to correct such failings have too often been limited to fine words; gross wrongdoing has sometimes been denied outright; penalties, where there has been a need for them, have rarely been sufficient to provide a real deterrent.

Many of the acts and omissions discussed here are criminal offences in some countries, only infractions of civil law in other countries, and in yet other countries are merely matters that some regard as unethical and that therefore demand ethical self-regulation. A purpose of Part III of the book is to suggest a policy on which kinds of unethical conduct should be criminalized. We argue for an important place for criminal enforcement, but one where the criminal law shows humility and deference at times to other legal, regulatory and self-regulatory strategies. Those events which have resulted in identifiable harm will call for adequate compensation through the machinery of civil courts or tribunals. Above all, however, there is a pressing need to identify much more effective tools than have hitherto existed to persuade industry to remain on a socially acceptable course. Society has been patient too long, and far too much unnecessary injury has been suffered. It is surely time to reach out a friendly but firm hand to the pharmaceutical industry and proceed resolutely to action.

During the 1960s and 70s constructive criticism of what was happening began to emerge from various quarters; the names of Charles Medawar, Ellen 't Hoen, Andy Chetley, Sidney Wolfe and Andrew Herxheimer deserve particular mention. Within the World Health Organization, Halfdan Mahler and Ernst Lauridsen developed a clear global basis for policy. From Australia, David Henry, Ken Harvey and Peter Mansfield provided bold leadership on various fronts. We must also acknowledge our debt to others who over the years have inspired us by their example, while some have contributed directly to our present analysis. We would mention in particular the research on the pharmaceutical industry by Fred Abbott, Marcia Angell, Peter Drahos, Philippe Guerin, Ane Haaland, David Healy, Joel Lexchen, Donald Light, Mark Mildred, Philippa Saunders, Dan Sigelman and Barbara Swartz, as well as the late Milton Silverman.
In approaching our subject we have chosen to present in Part I a single account of personal experiences that may help to explain our approach to truth and justice in this field; Graham Dukes has seen the industry from within but also from the standpoint of the regulator and policy maker, and in his Essay he describes the manner in which over the years his view of the world of medicines evolved.

In Part II, Graham Dukes leads the authors in considering pharmaceutical rights and wrongs as they have developed, particularly over the last half-century. We examine in turn each of the main facets of the pharmaceutical industry’s role in society – research, manufacturing, information, distribution and pricing – as well as some questionable aspects of this industry’s relationship to society.

Finally, in Part III, John Braithwaite leads the team in looking towards the challenges of the near and more distant future and the opportunities for reform. Past successes and failures in dealing with what is commonly termed “big pharma” provide some guidance as to future policies; above all, however, there is now a need for new thinking and fresh approaches. The foundations for a radically new course have already been laid by researchers in the social sciences. Concepts of responsive regulation, the complementary role of supports and sanctions and the mobilization of private initiatives to bolster enforcement are now well-defined and within our grasp. These are no castles in the air but the fruits of concrete innovation and empirical research.

In building this book, Graham Dukes and John Braithwaite have been generously supported by the critical and informed voice of James Moloney, a public health specialist who during the course of writing this book acquired practical experience in developing and developed economies. James started out with the team as a research assistant. His contribution became so central and pervasive that he became a co-author. James’ co-authors are grateful for his scholarship, his personal character and integrity and his unwavering commitment to the project.

Finally, the three of us would like to thank our families and institutions for their support, especially Dr Elisabet Helsing, the University of Oslo, the Australian National University and the Australian Research Council; Kylie McKenna and especially Kate Macfarlane for her capable and dedicated administrative, editorial and research support. We also thank our extremely patient and helpful colleagues at Edward Elgar.

Graham Dukes
John Braithwaite
James Moloney
PART I

Setting the scene
Introduction

A TALE FROM THE INSIDE AND A VIEW FROM THE EDGE

On a spring day in 1960 I found myself on a Dutch train, bound for the German frontier, in the company of an Irish-American physician. Both of us worked for our respective divisions of a venerable drug company with its offices in North Carolina. I myself, newly qualified in medicine and law, was still feeling my way as a novice in the unfamiliar world of pharmaceutical commerce, from the vantage point of a desk in Rotterdam around which the channels of business frothed and flowed. My travelling companion held a medical directorship with the parent company. Now he was on his way to a vital meeting in Germany; I was merely there to speed him on his way to the border. His mission, as he confided in me with some pride, was to secure a licence for North America on a major new pharmaceutical, a revolutionary sleeping remedy. Devoid of unpleasant effects, it could be used with confidence by the ill, the aged, by children, by women in pregnancy. As the train slowed for the border station at Nijmegen, he waxed ever more enthusiastic. I took my leave of him as we changed trains, very prone now to believe that I had been privileged to glimpse the dawn of a wondrous new era. Insomnia, I knew, was a plague of the city masses. Was the solution now indeed so close at hand?

Back at my steel desk in Rotterdam, the medicines on which my daily duties centred were more mundane. For the moment there was little more to demand my attention than a series of famous old remedies for relieving coughs and colds; even the most astute of the advertising people with whom I worked could not find a great deal of excitement in them when addressing messages to the public. But there were delightful individuals on every side - my colleagues, the extroverted advertising folk from Madison Avenue who flew in to disburse American experience in promoting commerce, the good-humoured production engineers with their weighty protocols. Even a life that for the moment was centred on cold rubs and cough syrups (though with promises of appetite suppressants, bone replacement materials and a wondrous cholesterol-reducing
drug yet to come) was in that way enjoyable, if not tremendously serious. All the people around me had wives and children and dogs and cats and they found the business exciting, if only because there was a competing cold rub being sold down the road and it would be fun to get the better of it. True, they found it tempting now and again to stretch the truth a trifle (anguished mother portrayed in advertisement: "Is it perhaps my fault that my baby still has a cold?"), but there was no wickedness, just a degree of mischievousness. Yes, the British daughter company had quietly started adding morphine to its over-the-counter cough syrup, but that was surely only a temporary aberration, and Whitehall was bound to stop them sooner or later. And yes, the people in the Canadian branch were about to be prosecuted for claiming (with a dubious quotation from Linus Pauling) that the mere trace of vitamin C that they put in their sugary cough drops would cure the common cold; but we in Rotterdam considered ourselves too sensible to do anything quite like that.

Sheer boredom with coughs and colds, and the slowness with which my promised research tasks developed, led me only months later to move to another company, this time a European pillar of industrial respectability with a solid research base. Yet from time to time I had reason to look back to the point where I had experienced my first encounter with the pharmaceutical industry – look back and sometimes wonder. First there were the black newspaper headlines now emerging about that exquisite sleeping remedy to which I had once been introduced in a train; hundreds – and in due course thousands – of children in Germany and elsewhere had been born without functioning arms and legs after their pregnant mothers had taken the drug. My one-time companion in the train had managed to slip the drug onto the Canadian market, with similar tragic results – heaven be praised, the Food and Drug Administration had stopped it in America before it had a chance to do any harm on that side of the border.¹ And then there was that cholesterol-reducing drug – could it be true, as the journals were now reporting, that the American company’s researchers had detected its horrifying side effects in laboratory animals, and had promptly destroyed the animals to be rid of the inconvenience?² Unfortunately it was true. My one-time employer, for whom I had known true affection, faded from the scene in a haze of doubt and disgrace, soon to become a mere branch of a soap company. Somehow, looking back to that time, I am reminded of Mr Justice

Sheen's verdict on that horrific disaster involving the Herald of Free Enterprise car ferry off the French coast in 1987: "the body corporate was infected with the disease of sloppiness". They say that cleanliness is next to godliness; perhaps sloppiness is next to wickedness; somehow, I had nearly brushed up against it.

My next 11 years were spent in the generous arms of the serious Dutch pharmaceutical company that was my new home, advancing on my way until I was awarded a senior medical and scientific post. The elderly Austrian professor who had blessed my initial appointment was a man of enviable repute and great achievements – but was the twinkle in his eye not a clue to some innate mischievousness on his part too? The years brought worthwhile scientific achievements to the group which I managed and I believe that we well deserved our success. With our horizontal form of management – shifting potential medicines almost seamlessly from the chemical laboratory to the pharmacologists and thence on to the clinicians – we surely attained more than one could ever have managed in a compartmentalized university environment. But as my ageing mentor retired and the bright-eyed young men from the business school moved into the oak-panelled offices, it was as if the curtain that shielded us in our cosseted research world from all that was vaguely improper or frankly sinful sometimes seemed to be growing very tattered.

Some of the new arrivals in and around the boardroom were honest salesmen whom I could respect. But others caused much headshaking in my circle. Flexible ethics … naughtiness … mischievousness … sloppiness … Was there perhaps a slippery slope close at hand? There was soon a tale going the rounds about our agents selling appetite stimulants to starving children on the Indian subcontinent ("Not with our specific approval, naturally, but it's difficult to set hard and fast rules for these things, you know."). Then there was the day when an untruthful draft advertisement that I had firmly turned down somehow slipped through to the printers ("So sorry, but you were out of reach that week"). And then there were those troublesome dogs that developed tumours when taking one of the company's best-sellers – somehow both they and the laboratory protocols that belonged with them were quietly spirited away behind my back into that distant other-world where inconvenient ("but quite possibly misleading!") reports are said to belong. It was time for me to move on.

If my subsequent decade in the world of national drug regulation taught me anything, it was that the faces of industry are so very diverse.

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Facing one firm after another at hearings across the green baize table, it was rewarding to meet first-class industrial researchers who had truly helped to relieve the lot of sufferers from Parkinsonism, glaucoma or hypertension. As government regulators, we were often respected by such people and our role appreciated. Yet there were also the figures who set out to bamboozle us; they seemed to live in the naive supposition that since we were mere civil servants who had never been to a proper business school we could easily be led up the garden path – or perhaps even eased towards leniency by a small financial consideration? There were also the moments when all the might of big business thundered up to our table, indignant that we were standing in the way of some supposed scientific breakthrough, and ready to drop dark hints of recourse to the minister if we persisted in our foolishness. We did indeed make the occasional mistake, but over the years a succession of ministers supported our judgements and we saved a lot of lives, quite apart from protecting some businesses from the consequences of their own foolishness.

After a decade I moved smoothly from national regulation into the rarefied but rich atmosphere of the World Health Organization. I remember well the condescending smile with which some of my one-time colleagues in industry tended to look at WHO; for them it was a well-meaning organization with no teeth and little pushing power. True, it had been rendered tame from its very outset by those national politicians who shuddered at the thought of anything approaching supranational authority. Yet though it might be weak in terms of formal authority, it was wise, experienced and vastly influential in other ways. The emissaries of the global drug industry might still bluster and thunder at the conference table in Geneva against any proposal to endow the World Health Organization with anything resembling true power; but behind the scenes, and particularly through its six regional offices, WHO quietly provided drug regulators from Jakarta to Reykjavik with the knowledge and experience that they needed in order to act in the public interest.

In later years, working from a solid university base, I commonly found myself as an expert witness confronting industry across a court of justice in matters of apparent drug injury, more particularly in the United States. The story of Mrs Grundberg is one that will always remain with me.4,5 Living in Utah with her mother, to whom she was devoted, poor Mrs

Grundberg had chronic difficulty in falling asleep and her family doctor had prescribed her a novel hypnotic. I was familiar with the product; in my regulatory days in Europe, our committee had, to the hysterical indignation of the producer, resolutely removed it from the national market because it was clearly capable of inducing a dangerously psychotic state in a minority of users. Unhappily, Mrs Grundberg proved to belong to that wretched minority and, under circumstances which pointed all too clearly to cause and effect, she had taken the drug as prescribed and then in turn picked up a gun and shot her beloved mother eight times through the head. A criminal court dismissed a murder charge against her since she had acted under the influence of a toxic agent. The attorneys with whose aid she now sued the producer for damages had done their work in the company archives. It was documented up to the hilt that the firm had become aware of this serious side effect in the early stages of human study, but had neither warned of it nor sought to find a safe dosage level at which it would be unlikely to occur. What of the company’s lawyers, well paid to conduct an unenviable defence? There is an old saying in American legal circles: “If you can’t win on the facts, argue the law; if you can’t win on the law, argue the facts. If you can’t win on either, call the other lawyer names.” Without a leg to stand on, as regards either the law or the facts, they adopted the third course, and sought to frighten me away from the witness stand with a barrage of veiled threats, scorn and insults. It was to no avail: Mrs Grundberg won a worthy settlement, as did a series of other victims who took the firm to court. It was not the pharmaceutical industry’s most glorious day. And yet ... Look back to the press records of the time and you may actually wonder whether in the long run virtue indeed prevailed. The firm found grounds to sue one of Mrs Grundberg’s witnesses for libel, and won in a British court. The convoluted press releases that followed portrayed the producer as a knight in shining armour who had been wronged throughout. Truly, public relations can be a mysterious art, setting truth about with many curious fictions.

Mischievousness ... naughtiness ... sloppiness ... foolishness ... plain wickedness – they can be hard to distinguish from one another, and the slope is indeed slippery. I have never, in the course of my various careers to date, found myself regarding the pharmaceutical business – or indeed any other acknowledged form of business – as essentially wicked,

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let alone criminal by nature. The slippery slope is however all too apparent, and it is particularly steep where competitive business is conducted on a massive scale with the prospect of large profits, and where the ultimate customers for whom the battle is being waged are distant and anonymous.

It is hardly possible, when considering the darker side of a field such as this, to confine oneself strictly to acts and omissions that lie only within the defined scope of the criminal law. That law differs from country to country and from time to time. The inability to bring a successful prosecution in the case of the *Herald of Free Enterprise* ferry disaster was understandable in view of the state of English law at that period. The outcome might perhaps have been different had Britain’s later Corporate Manslaughter and Corporate Homicide Act\(^7\) been in force at the time, though where large firms are concerned it may still be impossible to determine at which level of authority liability can be considered to lie.

No one whose interests and qualifications lead him or her to seek a career in the pharmaceutical industry, as I did many years ago, need hesitate to do so on the grounds that one may have to face ethical or legal challenges in the course of one’s work. The essential point is to recognize those challenges when one encounters them and at that point to stand firm on the side of righteousness. At a point in my own career when I was still very much committed to the industry, I published what I saw as a credo for any proper drug company, followed by one for myself:

> The fact that I shall ordinarily speak no ill in public of the firm to which I am attached is less a matter of rules than of acquired loyalty and conviction. If I encounter something with which I am not entirely comfortable, the first thing I shall do is to try and put it right. And nothing and no-one can prevent me at any moment from stepping out of the industry, if I feel the need to do so ...\(^8\)

That, surely, is a fair approach for anyone who chooses to share a journey with the pharmaceutical industry; but the adherence of individual staff members to such a creed also provides a vital anchor to social morality for industry itself. The behaviour of a corporation is not determined only in oak-panelled offices; it is shaped in large measure by the ideas, convictions and self-discipline of those who serve or advise it in many

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\(^7\) United Kingdom, Corporate Manslaughter and Corporate Homicide Act (2007).

another capacity. These things, perhaps to a greater extent than laws and regulations, will surely determine the extent to which the pharmaceutical industry deserves a place as a respected and respectable element in society in the coming decades of the twenty-first century.
PART II

A view of rights and wrongs
1. Creating a medicine: Why, how and how not

1.1 MEDICINES: GOOD, BAD AND MEDIocre

Throughout history, people have longed for newer and better medicines. For many centuries the principal source of remedies was the plant world; some of the medicines traditionally derived from plants have been adopted into modern scientific medicine; others, when tested methodically, have proved disappointing. The herbal tradition has by no means been fully explored but the quest continues; artemisinin, long used in Chinese medicine — in the form of a preparation of the plant artemisia annua — has for example in recent years been developed as a major tool in treating malaria. It was however the emergence of synthetic chemistry in nineteenth century laboratories that opened much wider perspectives, enabling entirely new substances to be created for medicinal purposes. During the last century and a half, much progress has been made towards meeting such needs, yet we still have far to go.

It is good that, across the world, many thousands of people are engaged in devising and developing better ways of curing illness and relieving suffering. Unavoidably however, as in any other field of endeavour, there have been disappointments and errors on the way, as well as a degree of improper dealing.

The rights and wrongs of behaviour in any field can only be judged if one is clear as to the standards by which it can be assessed. Those standards are likely to exist both in the form of very general principles on which there is wide agreement and as specific rules that are intended to put those principles into effect. When, to put it in very basic terms, does a drug — be it new or old — deserve a place on the pharmacy shelf? If we are happy to accept an answer in equally general terms (and to set aside for the moment issues such as pricing) then the answer can be expressed very simply: a medicine is acceptable in the community if it is both efficacious and safe and is of acceptable quality. Digging a little more deeply into the matter, however, one soon realizes that neither of these terms is absolute. Even the best medicine, whether it be a cough syrup or
an antibiotic, will not work in every patient or in all circumstances.\footnote{Connor S (2003), 'Glaxo chief: our drugs do not work on most patients', \textit{The Independent}, 8 December.} As to safety: even the most reputable pain reliever might on some rare occasions cause a user to develop a blood disorder or even to drop dead on the spot. Efficacy and safety are therefore relative concepts; we can better declare that a medicine must be \textit{reasonably} effective and \textit{sufficiently} safe in normal use. There must also be something of a balance between these two basic standards; if a new drug proves to cure a hitherto untreatable infection, one may be prepared to accept the fact that it induces certain side effects which society would not tolerate if it were a mere antacid. The interpretation of such principles is however bound to vary as society changes. It has for example been suggested that, since the rising incidence of obesity must itself be regarded in the twenty-first century as endangering public health, the community may today be more willing than in the past to accept the extensive use of drugs to depress appetite, since non-drug approaches to the problem, while carrying no risk at all, may in some cases be less effective.\footnote{Simeonidis S (2012), quoted by Berkrot B and A Yukhananov (2012), 'FDA OK's first obesity drug in 13 years', \textit{Chicago Tribune}, 27 June.}

In addition, however, our expectations and our demands in these matters have been raised progressively as medicine and science have moved forward. For many centuries, the community was prepared to live with a range of herbal remedies the reputation of which was based upon tradition rather than on firm evidence. That is much less the case at the present day; science in these matters may not be perfect but as a rule it brings one much closer to the truth than does any other approach. Studies of medicines, old and new, particularly in experimental animals, human volunteers and patients, are today considered to be of fundamental importance in determining whether a given medicine can reasonably be expected to provide relief or cure and to do so without exposing the user to unpleasant risks or unacceptable dangers.

So far, so good. Medical science, working hand in hand with an ambitious industry, has developed an impressive ability to develop potential new drugs, to define their properties, and to select those that indeed appear to merit a place in the consulting room and the pharmacy; at the same time, laws, regulations and other sources of standards intended to protect the public from avoidable risk have been developed. How is it, then, that over the years the newspaper headlines have so often pointed to dramatic and often tragic events following the use of newer or older medicines? As medicine and science progress further, can these
disasters not be eliminated? We do have at least some valuable pointers as to what can go wrong, and thereby some clues as to where society in these matters should be capable of doing better. It is nevertheless important to bear in mind that, however extensive the studies carried out with a new medicine to define its properties before it enters the market, they provide no more than a fair prediction of its ultimate value. Once it has come into widespread use in a heterogeneous population, surprises may well emerge, causing one to redefine its usefulness and even its acceptability; a manufacturer, a regulatory agency or both may find reason to reconsider their views on a medicine after it has been marketed for a time, and drug withdrawals are as a result not uncommon. 3

1.2 THE EMERGENCE OF STANDARDS

Today, medicines are brought to the market almost exclusively by the pharmaceutical industry. Even in those instances where a product has originated in academic research or has been inspired by traditional or herbal medicine, the process of defining its properties, to the point where it is eligible to secure marketing approval by reputable drug regulatory agencies, will as a rule be undertaken by a pharmaceutical firm or subcontracted by it to others. The regulator will demand, at the most basic level, evidence of the nature and quality of the product (Chapter 2). Beyond that, however, the community’s main concern will be whether the medicine will generally serve its intended purpose or purposes. Can it reasonably be regarded as effective in one or more well-defined conditions? Is its mode of use adequately documented? Is it sufficiently safe for use in every situation where it might be beneficial? And, since any medicine is virtually certain to produce adverse effects or to interact unfavourably with other substances, have those risks been sufficiently well delineated to conclude that they are acceptable – and perhaps, with due care, avoidable? Each of these fundamental questions is likely to lead on to others that will need answering if the place of the product in medical treatment is to be sufficiently circumscribed to guide the doctor and the patient in using it. Other questions will be concerned with identifying the contraindications (meaning those situations in which the

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medicine should not be used if undue risk is to be avoided) or the possible interactions with other drugs or products. In all these matters the view has taken hold that it is the originator or manufacturer of a medicine, standing as it does to gain financially from its acceptance and sale, which is primarily responsible for meeting the standards currently in force.

The principles that apply today to the evaluation and approval of medicines for efficacy and safety have been extensively defined; they are to be found in the rulemaking of both national and international drug regulatory bodies. It cannot be said that the definition of standards is exhaustive or ever will be; as new types of remedies emerge or unexpected problems present themselves, new or adapted rules will be needed to deal with them. Nor are the rules entirely consistent from one part of the world to another. Populations differ, but so do the views of experts and the nature of disease. In broad measure, however, contemporary standards for demonstrating that a drug is sufficiently efficacious and safe for use are widely agreed between scientists and are reasonably similar from one country or region to the next. Such variations as exist rarely cause serious problems. There is however a place for some flexibility; even where standards are identical, the stringency with which they need to be imposed can vary. A set of published principles for the demonstration of efficacy or safety is therefore no more than that; they are not precepts set in stone, nor yet are they mere starting points for negotiation: they indicate the broad lines along which experts working with one another should be thinking and which need to be respected when scientific decisions are taken. Any experienced regulatory agency, looking back on its performance during a single working session, is likely to find that it has applied the basic principles to 20 different drugs in somewhat different ways. It is also likely to conclude that in the great majority of instances there has been no fundamental difference of opinion between the scientists from the agency and those representing serious industrial applicants as to the way in which, in a specific instance, the rules should be interpreted and applied, though there may be a deal of lively negotiation on the way. One can indeed recognize a degree of "game playing" between the regulator and the regulated as published standards are interpreted with respect to an individual drug product, but it

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4 See, for example, Abbott FM and Graham Dukes (2009), 'The global regulatory environment', in FM Abbott and Graham Dukes (eds.), Global Pharmaceutical Policy: Ensuring Medicines for Tomorrow’s World, Cheltenham, UK and Northampton, MA, USA: Edward Elgar, pp. 86–115; see also Section 1.4 below.
is as a rule a game responsibly played by experienced parties with the public interest in mind.

1.2.1 The Creation of Standards

This situation, in which society’s reasonable expectations and needs are laid down in the form of standards which a drug provider is expected to meet, has only been attained with the progressive emergence of formal drug regulatory systems across the world, mostly in the course of the twentieth century. Before that time, medicines were merely subject to whatever standards were considered applicable in civil or criminal law to the sale of goods generally. In English law, for example, false warranties given by a seller regarding goods of any sort were regarded as a valid cause of action as early as 1382 when the purchaser of a horse warranted to be “sound in eye and limb” found that it was in fact blind. Over time, however, the practice of the courts showed that they were hardly interested in determining whether the seller had deliberately set out to deceive; the essential issue was whether the buyer had in fact been deceived or not. Such protection as the law afforded to the purchaser was in any case limited to situations in which a warranty had been given. If there were no explicit warranty, the question for a court would be whether the buyer had made a sufficient effort to protect himself (“caveat emptor” – let the buyer beware). As one learned writer put it in 1534, with respect to the sale without warranty of a cask of wine or a horse, “... the other must buy it from him at his own risk, and his eyes and taste should be the judges in that case”. The courts did however recognize that even critical purchasers might on occasion suffer ill consequences that they could not reasonably have foreseen, for example if they became ill after consuming food or wine that had not appeared to be defective when it was bought. From the fifteenth century onwards, English statute law had indeed laid an obligation on the sellers of foods to provide “wholesome victuals”; breach of this law could lead to prosecution in a criminal court. It was not however until 1893 that comprehensive legislation was enacted in England setting “merchantability” and “fitness for purpose” as implied conditions on the sale of any goods, even in the

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5 Aykesbury v. Watts (1382) Y.B. 6 Ric. II.
6 Fitzherbert A (1534), Natura Brevium, fo 94C.
absence of warranty, and where a party had breached its terms this Act provided a basis only for civil remedies.

None of these developments in legal principles was sufficient to deal adequately with the manufacture and sale of medicines. It had long been recognized that no medicine could be expected to prove effective in every case in which it was used, and that treatment could bring with it unwanted complications; therapy was commonly a matter of choosing between a series of almost equally unsatisfactory alternatives. It was therefore impossible, so long as no true science of therapeutic evaluation had developed, to define what in this particular field would be meant by terms such as "merchantability" and "fitness for purpose". All the same, there were instances in which a methodical attempt was made to acquire reliable data regarding the efficacy or safety of a medicine. When the English physician William Withering in the late eighteenth century observed that an old woman practising herbalism in Shropshire was successfully treating dropsy (cardiac oedema), he carried out a series of well-thought-out experiments in patients to determine which of the various herbal components she had used was responsible for the therapeutic effect. His systematic work led him to identify the digitalis leaf as an effective treatment for heart failure. With the development of organic chemistry in the next century, followed by the emergence of a true pharmaceutical industry, further serious attempts were made to apply scientific knowledge to drug development and assessment. Justus von Liebig in Germany synthesized and tested both the sleeping remedy chloral and the anaesthetic chloroform in 1831. Both were subsequently found to be effective and sufficiently safe for use in human subjects. Similarly, when the antipyretic agent antipyrine appeared in 1884 the clinical demonstration that it could relieve fever and pain opened up the era of the non-narcotic analgesics. Some attempt was also made to assess the toxicity of these new agents in animal studies. When acetylsalicylic acid was introduced in 1899 as Bayer Aspirin, an effort to determine how well it was tolerated involved administering it to rabbits and cold-blooded animals, as well as applying it to sensitive tissue in the form of

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9 *Withering W (1785), An Account of the Foxglove, and Some of its Medical Uses, Birmingham: Robertson.*


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the gills of two live goldfish. The tests were primitive, but Aspirin had fortune on its side, subsequently proving to be remarkably safe when it came into widespread use. The drugs in the antipyrine family unhappily proved capable of causing a blood disorder (agranulocytosis), one reason why society slowly came to realize that a great deal more effort might be needed to determine whether a new drug was sufficiently safe in actual use.

The notion that the community might need to exercise some form of supervision over the actual making of drugs had in fact arisen as early as the Middle Ages. In the Holy Roman Empire, the Edict of Salerno, as promulgated in 1241, set strict standards both for the growers of medicinal plants and for dispensing pharmacists. A French “Royal Ordonnance” of August 1343 forbade anyone to prepare medicaments unless he knew how to read a prescription and dispense, while in London in 1423 two apothecaries were appointed to inspect shops selling medicines “and bring any that offended in the quality of their wares” before the Mayor and Aldermen of the City. All the same, these and similar legal provisions, even as late as the nineteenth century when many countries regulated the profession of pharmacy, still started from the fundamental belief that traditional knowledge provided the basis for recognizing that a drug was medically acceptable. The need to regulate these latter matters hardly arose until entirely new drugs began to emerge from the laboratory. As late as 1906 the United States Federal Food and Drugs Act prohibited the sale of “adulterated” or “misbranded” food or drugs from interstate commerce but still set no standards for proof of efficacy and safety. Another thirty years were to pass before American law began to demand evidence against which the acceptability of a drug product and the claims made for it by its sponsors could be judged.

During World War I, a number of new organic arsenicals, notably arsphenamine (known commercially as SalvarsanR) came into widespread use for treating syphilis after their marked activity against the causative spirochaete had been demonstrated in laboratory experiments. Unfortunately, they had also been shown at an early stage to be highly toxic to

various bodily systems. The extent of the problems with the arsenicals was amply confirmed by a British government enquiry of 1922, but until the arrival of penicillin 20 years later no safer alternative treatment for syphilis existed. Since the adverse effects of the arsenicals had been documented so promptly and were unavoidable, society had to tolerate them and there was no question of any criminal liability attaching to their preparation, sale or use.

Such problems with entirely new medicines, coupled with an increasing concern about the widespread use of entirely ineffective and unproven "remedies" sold over the counter did ultimately persuade the health authorities in various countries to set official standards and procedures for the admission of drugs to the market. In Europe, Norway led the way in 1928, closely followed by Sweden.

1.3 THREE CLASSIC DRUG DISASTERS

The process, as well as the recognition that issues of both civil and criminal liability might in some cases be involved, was hastened by the occurrence of three classic drug disasters. Half a century or more later, all three merit brief consideration.

The first of these followed the introduction in the United States of an early sulphonamide – one of the first truly effective antimicrobial agents – which one manufacturer planned to market in liquid form. In 1937 the SE Massengill Company of Tennessee decided to introduce sulphanilamide in the form of a pleasant-tasting liquid remedy for sore throats ("Elixir of Sulfanilamide"). The solvent was to be diethylene glycol, which had been known since 1859; it had an acceptable taste and colour and offered the benefit of low cost since it was already being mass-produced for industrial purposes and as an antifreeze for cars. It had not however been tested for safety when taken internally. In fact it was broken down in the body to oxalic acid, which is highly toxic to the

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17 MRC (1922), Reports of the Salvarsan Committee: II – Toxic Effects Following the Employment of Arsenobenzol Preparations (Medical Research Council), London: His Majesty's Stationery Office.
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kidneys. The Elixir was marketed and within a short period 107 deaths were documented as a consequence of its use. The firm’s chief chemist committed suicide. The head of the firm initially told reporters: “my chemists and I deeply regret the fatal results but ... I do not feel that there was any responsibility on our part”, yet he subsequently pleaded guilty in a federal court to 112 counts under the Federal Food and Drugs Act of adulteration or misbranding of the product. Massengill was consequently fined a total of $16,800. *Time* magazine reported later that the Company had also spent more than $150,000 to settle damage suits brought by victims of the Elixir or their families. Good examples of an adequate community response to a drug accident in one country are not necessarily emulated elsewhere; 70 years after the events in the United States, diethylene glycol was still being used as a drug solvent by unscrupulous firms in a number of developing countries (see Section 1.10 below).

As a direct consequence of the Massengill case, the 1906 Food and Drug Act, which provided for prosecution only in cases of fraud, was quickly replaced by the Federal Food, Drug, and Cosmetic Act of 1938. Under the new legislation, fraud no longer needed to be proved when prosecuting those making false claims for drugs; however, scientific proof of safety was now required before new drugs could be marketed, and federal court injunctions to suppress violations were given legal force.

World War II, though it stimulated new lines of drug research, delayed the further development of standards. When the movement resumed it was very much as a reaction to two further cases, this time centred on Europe.

The injury done by Stalin on, primarily in France, illustrated the dangers of reckless amateurism in both the design and manufacture of medicines. The Paris pharmacist Georges Feuillet found himself suffering from furunculosis (boils) and working on the hypothesis that diiodoethyl tin might favourably affect this and other skin conditions, he formulated a combination of this compound, supposedly in a 15 mg dose with added vitamin F. His own condition appeared to respond well, as did some cases treated by an acquaintance in a military hospital. Drug approval in France at the time was based largely on the submission of satisfactory

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testimonials to the Ministry of Health. Permission to market the formulation through a drug company was soon obtained and under the name Stalinon it was promptly introduced in both France and North Africa. After some months, cases of sudden death among users, characterized particularly by massive oedema of the brain, were being reported on all sides; the number of fatalities soon exceeded a hundred, while many other patients suffered severe injury. M. Feuillet faced both prosecution and massive civil litigation. In court an expert witness pointed out that the tin compound that had been used was well known to be both unstable and highly toxic.\textsuperscript{22,23} There was also much doubt as to whether the work that had been carried out with Stalinon was scientifically valid. The clinical study, such as it was, had been performed with capsules which because of a dispensing error contained only 3 mg of the active compound. Animals appeared to be much more resistant to the toxic effects of these tin compounds than were human subjects, and since the toxic effects of organic tin appear only after prolonged administration, acute toxicity studies would fail to detect them.

The Stalinon case had occurred despite the fact that the requirements for drug approval were at the time rather more extensive in France than in most other European countries. The case highlighted the need for strict inspection and for appropriate studies of efficacy and safety. In addition, the Stalinon case showed that France's "recognized experts", a group of physicians designated as such because they were considered capable of providing testimonials regarding efficacy and safety on the basis of simple observation, had failed to represent the public interest adequately. Their role was in fact already becoming outdated with the development of advanced methods for evaluating drugs in human subjects by Bradford Hill and others.\textsuperscript{24} The "randomized double-blind controlled clinical trial", in which an experimental drug was compared objectively with a known compound, a placebo or both, had by mid-century become a major tool in determining the efficacy and safety of a medicine.

It was notable that many well-established pharmaceutical companies, in France and elsewhere, had at the time already advanced well beyond the inadequate standards of drug development that had enabled the Stalinon disaster to occur. On the other hand even well-established principles, such as the use of placebo comparisons, were on occasion challenged where these appeared likely to impede commercial interests.


\textsuperscript{23} Anon. (1957), 'Medicine: the killer drug', \textit{Time}, 30 December.

This was typically the case as regards the study of antidepressant and anxiolytic drugs, the value of which was often rather less than originally proposed: Khan et al. reviewed in 2002 data suggesting that conventional psychopharmacological agents for depression and anxiety were superior to placebo less than half the time; elimination of placebo comparisons would therefore be very likely to result in the introduction or survival of certain drugs which in many cases would show little true efficacy or none at all. Other data have led to similar conclusions.

Unfortunately, the thalidomide disaster that followed only a few years later seemed to show that such accidents could not always be ascribed to the recklessness of amateurs; they could also occur with products developed by relatively sophisticated firms. The case also provided a reminder that it would not always be feasible to provide adequate proof that a drug was safe through pre-marketing studies alone. Developed by the Grünenthal Company in Western Germany, thalidomide (known commercially as Contergan or Softenon) was intended as a sedative and hypnotic. Structurally it was not so different from some existing sedatives as to suggest that unforeseen problems might arise in its use; that very fact may have led to a somewhat cavalier approach to issues of safety. The company had however earlier sought to market a derivative of penicillin that soon proved to be substantially more toxic than the parent compound, as well as a tuberculostatic drug that turned out to be entirely ineffective, so in that respect the firm should have been well aware of the need for caution. After trial marketing in 1956 as a supposed remedy for respiratory infections, thalidomide was introduced on a massive scale in Germany in October 1957 and licensed in many countries as a sedative, formulated either alone or in combination. The United States FDA resisted approval for marketing in the light of increasing evidence from the field that the drug was toxic to the nervous system, but the agency also posed questions regarding its safety in pregnancy. The latter issue was to prove crucial. From October 1960

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28 Notably Doriden (glutethimide) sold by the Company known at the time as Ciba.
onwards, a series of German doctors repeatedly reported the birth of infants with seriously deformed or underdeveloped limbs, a condition known as phocomelia, which had been described in the nineteenth century but had hitherto been excessively rare. Among the independent physicians who set out to find a cause for what soon appeared to be a developing epidemic of the condition was the paediatrician Widekund Lenz of Hamburg, who after some time determined that most, if not all, of the mothers concerned had used thalidomide during their pregnancies. He cautiously reported on the apparent link between thalidomide and phocomelia to a meeting of paediatricians on 18 November 1961. With similar conclusions being received from other sources, Grünenthal withdrew the drug only a week later, blaming pressure from the media as its reason for doing so and without admitting any causal connection between the drug and injury to unborn children. Ultimately, several thousand cases of thalidomide-induced phocomelia were reported from various parts of the world.\textsuperscript{29,30}

While in retrospect the company that developed, marketed and licensed thalidomide is universally regarded as having been responsible for much of the injury that it caused, its primary failings were not with respect to its failing to detect in advance the adverse effects on the unborn child. Some medical experts of the day indeed believed that the unborn child was in some way immune to toxic influences;\textsuperscript{31} there are in any case obvious ethical difficulties which stand in the way of carrying out trials of drug safety in pregnant women. And while the pre-clinical testing was undoubtedly "superficial and incomplete",\textsuperscript{32} later work showed that most species of animals in routine laboratory use provided poor models for predicting the appalling effects of the drug in human pregnancy. Grünenthal’s principal fault must be considered to have lain in its strenuous efforts to discredit the emergent evidence from the field that thalidomide was doing appalling harm.

One must add that, although numerous civil claims for damage were brought against Grünenthal and its licensees and settled out of court,

\textsuperscript{29} Lenz W (1992), \textit{History of Contergan (thalidomide)}, Lecture to the 1992 Congress of UNITH (Union Nationale pour l'Insertion des Travailleurs Handicapés).

\textsuperscript{30} It may be noted that in later years thalidomide was reintroduced for a very specific indication (treatment of leprosy reactions).

\textsuperscript{31} Uzerman GL (1960), ‘Personal statement to MNG Dukes’ (unpublished notes).

there was never a successful prosecution of the company or its employees. A criminal trial brought in Germany was abandoned after nearly a decade of preparation and hearings following a convoluted defence; reasons for its abandonment were stated to include the stress inflicted by the lengthy proceedings on those involved and the fact that Grünenthal had in the meantime agreed to numerous settlements out of court. As Sjöström and Nilsson however commented after an exhaustive study of the proceedings: "The court's final position leaves no doubt that most of the charges originally brought against Chemie Grünenthal by the prosecution were considered to have been legally substantiated".

1.4 THE BASIS OF CURRENT STANDARDS

The three historic cases outlined above provided much of the impetus that emerged in the mid-twentieth century to develop better standards for assessing the efficacy and safety of new drugs and re-examining the merits of those already marketed. Many new standards found their origins in the increasingly sophisticated regulatory structure adopted in the United States as the century progressed, in national legislation in Europe from 1958 onwards, in industrial manifestos, and ultimately in regional and multinational agreements covering a great part of the world. The World Health Organization (WHO), despite its lack of legislative power, has done much to create norms; in such matters, WHO has towards member states played the role of a wise and

33 Teff H and C Munro (1976), Thalidomide, the Legal Aftermath, Farnborough: Saxon House.
38 International Conference on Harmonization, available at http://en.wikipedia.org/wiki/international: Conference on harmonization of technical requirements for registration of pharmaceuticals for human use. The work of the International Conference on Harmonization, a major source of detailed standards, is based on input both from major regulatory agencies and from industry.
39 See for example Jayasuriya DC (1985), Regulation of Pharmaceuticals in Developing Countries, Geneva: World Health Organization; and many other documents.
benevolent uncle and has struggled to maintain its independence in such matters despite partisan pressures (Chapter 4). Regulatory standards have sometimes been enacted in the face of strong opposition from parts of industry, but in recent decades there has been an increasing, though not complete, degree of consensus.

A brief summary of the principal phases in the research and development of a potential new drug will be found in Box 1.1 below. New drugs may come from various directions, but many will have been synthesized in a chemical laboratory on the basis of a theory that a particular structure might have useful effects in treating illness. There is no rigid distinction between research and development; "research" is essentially designed to find out whether the new compound does indeed bear promise; if the results seem positive, "development" will follow to confirm these findings and build up the knowledge that is needed if the drug is to be officially approved and marketed. Box 1.1 is naturally no more than an outline: the process can be lengthy and because drugs vary so much in their nature and uses, the exact approach will vary from case to case.

Any examination of the duties imposed on (or recognized by) the pharmaceutical industry with respect to efficacy and safety, irrespective of whether it is undertaken as an academic exercise or before a court of civil or criminal law, can thus draw upon a great many authoritative sources and precedents. Quite apart from the above regulatory standards and recommendations one can refer to the great mass of civil litigation in which these issues have arisen and judgments have been handed down that reflect closely the need to respect these same standards. As was the case with Stalinon, civil litigation and criminal prosecution often run in parallel. A manufacturer which has conformed to an agreed statutory standard will be better placed to offer a credible defence should it be faced with civil litigation.

The fact that a firm seeking approval of a drug or a study fails to meet certain formal requirements naturally does not prove improper or criminal intent. Its acts and omissions may reflect negligence (though that may of itself, if gross, lead to criminal liability) or they may be attributable to plain human error or misunderstanding of the rules. Failure

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40 In Britain, Brian Cromie was speaking of the "mass murder activities of regulatory authorities". See Cromie B (1979), 'Present problems: the effects of British regulations', in Medicines for the Year 2000, London: Office of Health Economics. In 1984 a spokesman for Italian industry was quoted as declaring that drug regulation threatened to kill the entire Italian pharmaceutical industry. See Anon. (1984), 'Aleotti on "death" of Italian industry', Scrip, 905, 1.
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The presentation of seriously flawed data may mislead the regulatory authorities whose task it is to represent the public interest, or the prescriber who encounters this information in advertising material without recognizing its deficiencies; where direct advertising of medicines to the public is permitted, misleading data may improperly influence the lay person’s choice or use of a medicine. In any of these contexts the use of flawed material is culpable and potentially harmful.

BOX 1.1 MAJOR ELEMENTS IN THE STUDY OF SAFETY AND EFFICACY

Pre-marketing
1. Early animal studies (activities, acute/subacute toxicity)
2. In vitro studies (where feasible): effects on biological materials
3. Administration to healthy human volunteers (Phase 1)*
4. Controlled studies in patients (Phases II & III)*
5. Later animal studies (longer-term toxicity)
6. Special studies (e.g. interactions, effects in particular populations) as required in view of nature and uses of the product

Post-marketing
1. Longer-term controlled studies in patients as required (Phase IV)*
2. Pharmacovigilance (study of adverse reaction reports from field)

The "four phases" of clinical study were originally designated by the US Food and Drugs Administration and the classification has been widely followed. Phase I studies are intended to provide initial evidence of the effects of a drug in healthy human volunteers. If the results are promising, Phase II work will seek to define the effects of the compound in a limited group of patients, and Phase III extends this work to a larger patient population as a basis for seeking drug approval. The term "Phase IV" relates to follow-up studies after a drug has been marketed.
Standards have been developed for each of these phases. They include the need to examine the efficacy of a drug against the apparent efficacy of a placebo and the principle of double-blind studies in which neither the investigator nor the trial subjects are aware which participants have received the experimental drug and which have been treated with a reference substance or placebo. These standards had been widely accepted by 1960* and they have continued to evolve.

Note: * Cited from Fortune 500 estimates in 2005.

However extensive the definition of standards has become, there will always be situations of doubt and disagreement as to their interpretation. One such issue that comes repeatedly to the fore is the extent to which measures of acceptability as regards the efficacy and safety of a new drug should be influenced by the merits of products already available. To some extent that clearly must be so. If in 1930 a drug had been developed that saved lives in 20 per cent of cases of lobar pneumonia it might have been considered a godsend since nothing better was available. Fifteen years later, after the introduction of penicillin, such a drug would have merited no place in medicine; penicillin and its congeners had set a new and much higher standard for efficacy.

There are however many more subtle situations. Various writers, for example, have raised this issue with respect to the introduction of the so-called third generation oral contraceptives. The original products in this class, marketed by 1960, brought with them a significant risk of venous thrombosis, in some cases fatal. They were largely supplanted within a decade by a “second generation” in which the quantities of active components were greatly reduced so that the risk of thrombosis became insignificant. With the expiry of patents on the progestational components originally used, however, manufacturers seeking to maintain their prices and income introduced a “third generation” of contraceptives based on new progestagens. These offered no therapeutic advantages, but the risk of thrombosis was again raised, apparently by some 70 per cent. Civil claims brought by users or their families against the three manufacturers concerned failed in England’s High Court because of disagreement as to the level of statistical proof required.41,42

41 Anon. (2008), ‘Ontwikkelingen in anticonceptie’ (in Dutch), Geneesmiddelenbulletin, 42(11), 104.
In such an instance one is faced with the vexatious borderline between corporate behaviour that is merely unfortunate or improper on the one hand and that which must be considered immoral, antisocial or even criminal on the other. The fact is, however, that in the situation sketched above an unknown number of women who had used these “third generation” products were injured, and some lost their lives, as a result of an innovation that in fact served only to maintain industrial profits. Society’s view of corporate behaviour has perhaps not yet proceeded to the point where it is prepared to take a sufficiently firm stand on the matter.

Finally one must stress again the fact that a medicine considered acceptable at the time of its introduction may come to be regarded more critically in the light of new facts emerging in the field; a manufacturer must be considered under an obligation to keep abreast of new developments and adapt to them, whatever the consequences for the marketing of its products.

1.5 FAULTS IN THE DESIGN OR EXECUTION OF STUDIES

If a study of a drug’s efficacy or safety is poorly designed or badly carried out, it is likely to produce incorrect results that may mislead the investigator as well as the intended user. A reputable regulatory agency may be capable of detecting the fault and discarding the resulting data; a physician presented with the results as part of the drug’s promotion may on the other hand not have the experience or opportunity to do so. A weak study can all too easily produce a misleadingly favourable picture of a compound’s efficacy or safety, and a company may readily or unthinkingly ride the tiger of this doubtful work.

1.5.1 Design Errors

With the massive amount of expertise in the conduct of drug studies that has become available during the last 60 years, there can be no excuse for a badly designed investigation. Despite this, one repeatedly encounters defects in the planning of such studies. Some of these are detected when a drug is submitted for approval and the material is examined critically

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by experts; others are revealed only in retrospect when a medicine fails to live up to its promise and the original evidence is re-examined in an attempt to determine why this is so. When in 2006 a group of Danish investigators examined clinical studies sponsored by Pfizer involving two of the company’s antifungal drugs, they identified defects in the study design that undeservedly flattered the results for the Pfizer product as compared with the reference drug. To quote their summary of the findings literally:

We have previously described how a series of trials sponsored by Pfizer of its antifungal drug, fluconazole, in cancer patients with neutropenia handicapped the control drug, amphotericin B, by flaws in design and analysis. We describe similar problems in two pivotal trials of Pfizer’s new antifungal agent, voriconazole, published in a prestigious journal. In a non-inferiority trial, voriconazole was significantly inferior to liposomal amphotericin B, but the authors concluded that voriconazole was a suitable alternative. The second trial used amphotericin B deoxycholate as comparator, but handicapped the drug by not requiring pre-medication to reduce infusion-related toxicity or substitution with electrolytes and fluid to reduce nephrotoxicity, although the planned duration of treatment was 84 days. Voriconazole was given for 77 days on average, but the comparator for only 10 days, which precludes a meaningful comparison.43

In the worst case, a pharmaceutical company may fraudulently design a study to produce an apparently convincing result. Particularly where a comparator drug has been administered in a low dosage or only briefly one may have reason to suspect that the methodological fault has been intentional.

1.5.2 Faults of Execution

In other instances a firm may in all innocence present to the authorities or to prescribers an investigation that has been misleadingly or incompetently conducted or not carried out at all. It is unfortunately a fact that the pressure to identify investigators with whom research can be sponsored is such that a company may negligently engage the services or accept the findings of an investigator whose credentials they have investigated insufficiently or not at all. To cite a single example, taken from a newspaper report in the United States:

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If ever there was a wonder boy in the lucrative business of drug testing it was Dr Robert Fiddes ... Companies large and small showered him not only with more than 170 studies to conduct, but with millions of dollars in compensation for his work. But amid the glitter and cash was a fact that no one outside his office knew: It was all a scam. For Dr. Fiddes was conducting research fraud of audacious proportions, cutting corners and inventing data to keep the money flowing from the drug industry. Fictitious patients were enrolled in studies. Blood pressure readings were fabricated. Bodily fluids that met certain lab values were kept on hand in the office refrigerator, ready to be substituted for the urine or blood of patients who did not qualify for studies. Monitors for the Government and the industry never noticed any problems with Dr. Fiddes’s bogus paperwork ... Finally ... Dr. Fiddes and several accomplices pleaded guilty to fraud, drug-study results for virtually every company in the business were compromised and the reliability of the private system for testing drugs for safety and efficacy has been thrown into question.44

It is however only fair to add that some instances of falsification – of which very many more could be cited – have related to work entrusted by pharmaceutical firms to apparently reputable contract laboratories or even to academic institutions, and that the principals have in such cases often been only too eager to demonstrate their innocence of any wrongdoing. A classic case came to the fore in 1986 when the German company Schering found itself misled by reports on a study of one of its drugs, conducted by an apparently reputable academic investigator in Australia. The study in question related to an oral contraceptive marketed worldwide by Schering and purported to show that there were no adverse effects on the lipid spectrum. According to an account of the events published in the press at the time, “... much of the research as described and presented by Briggs never took place ... and in one paper he wrote up a study of dogs that he had not done.” Perhaps not inappropriately, an independent review of the events was published under the title: “Hark, Hark, the fictitious dogs do bark”.45

The objectivity of a study, whether conducted prior to approval or in the post-marketing phase, may also be in doubt where it has been conducted by investigators who are closely linked to the sponsor company or who have received disproportionately large rewards for their efforts: on a number of occasions this appears to have been at the root of

findings that unduly flatter the product in question. In 2011 the US Senate Finance Committee was reported to be examining this aspect of studies with the Medtronic product Infuse\textsuperscript{R} \textsuperscript{46} (see also Section 1.7).

Finally, one occasionally encounters cases in which an academic investigator has falsified work for no apparent reason. From 2000 onwards some uncertain evidence (in part from Wakefield et al.) came to the fore that the combined MMR (measles-mumps-rubella) vaccine used in children might be capable of inducing autism. In 2008 a further paper published in The Lancet by Wakefield et al. seemed to strengthen this suspicion.\textsuperscript{47} The publications led to a worldwide movement against MMR vaccination, and claims for compensation of supposed victims of this effect were lodged on both sides of the Atlantic, some being directed against pharmaceutical companies. In due course the bulk of the evidence appeared to disprove the supposed association; Wakefield and one of his co-authors were found to have falsified data and were guilty of other abuses. They were deprived of their right to practise medicine.\textsuperscript{48}

In 2006 it emerged that Dr Jon Sudbø, an investigator attached to Norway’s Radium Hospital, had falsified in every detail studies that he claimed to have conducted to examine a possible correlation between the taking of anti-inflammatory drugs, such as paracetamol, and the occurrence of oral cancer. According to the hospital’s strategy director: “He faked everything: names, diagnosis, gender, weight, age, drug use.” Various of the papers that he had published, some in prestigious journals such as the New England Journal of Medicine and Lancet, were retracted.\textsuperscript{49,50} Dr Sudbø’s supposed work was not stated to have been sponsored by any commercial firm.

While not reflecting on the pharmaceutical industry, the Sudbø case provides yet another reminder to any party sponsoring external research of the need to verify thoroughly the credentials and manner of working of all the investigators involved before entrusting work to them. In 2013

\textsuperscript{46} Reppeport A (2011), ‘Medtronic under fire over spinal bone product’, Financial Times, 29 June.


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GlaxoSmithKline, to its credit, stopped a clinical study in China of an experimental drug for multiple sclerosis and dismissed the principal investigator when it became clear that so-called data emerging from the work was in fact fictitious.51

Finally, one must regretfully observe that, even where a study has been designed and performed according to the rules, the sponsor may mask any undesirable findings before the result is presented to the authorities or made public – an issue that will be considered separately in Chapter 4.

1.6 WITHHOLDING OR MISREPRESENTATION OF PRE-MARKETING EVIDENCE

Almost without exception, national and regional systems of drug regulation require that a firm shall, in its dealings with the authorities, present the evidence relating to a drug fully and fairly. That requirement, primarily set with respect to the initial approval of a new drug, is now generally agreed to hold good also with respect to evidence becoming available subsequent to marketing (see Section 1.7). In both respects the record of the pharmaceutical industry has been found wanting, and over a period of half a century there seems to have been little sign of improvement.

In the book that preceded the present volume in 1984, Braithwaite presented the case of MER-29, marketed by the William S. Merrell Company up to 1961 as a means of reducing circulating cholesterol levels. Following its withdrawal in the light of injury to several thousand patients, including serious damage to vision, the Food and Drug Administration received evidence from a former laboratory technician at Merrell that similar adverse effects had been observed in studies carried out on monkeys, dogs and rats. The supervisor involved had duly withdrawn one seriously affected monkey from the study and replaced it with a healthy animal that had never received the drug. Records on seven other monkeys were changed to “smooth out” the data before a report was submitted to the FDA: evidence of blood dyscrasias in some of the other animals was deleted, as were data indicating damage in various species to the eyes, liver and gonads, while the fact that all the female rats in one investigation had died was removed from the record.52

In or about 1970, the Organon company's toxicological unit in the Netherlands found that one of its oral contraceptive products was producing mammary tumours in the female dogs used for long-term toxicity studies. The animals were destroyed and the relevant records deleted, the findings never being laid before the authorities.\(^{53}\)

The benzodiazepine-related drug triazolam (Halcion\(^R\)) was introduced by Upjohn as a sleeping remedy from 1988 onwards; its sales licence was suspended or withdrawn in a number of countries following reports from the field that in a proportion of users it could induce homicidal, suicidal or other deviant behaviour, at least in higher doses. In the United States a number of civil actions were brought against the manufacturer by persons who claimed to have suffered such effects; one such case is summarized in the Essay in Part I of this volume. The "discovery" process showed that, although clinical studies had clearly shown the ability of the drug to produce seriously deviant and dangerous mental behaviour, the manufacturer had suppressed these findings when reporting its research data to the authorities.\(^{54}\)

The tragic events relating to the marketing from 1999 onwards of Vioxx\(^R\) (rofecoxib) by Merck Inc. comprise one of the major drug disasters of recent years. The data are summarized in Section 1.7 below since at least part of the evidence of risk appears to have emerged subsequent to registration.

The antidiabetic drug rosiglitazone (Avandia\(^R\)), developed by Glaxo-SmithKline, was withdrawn or severely restricted in most markets from 2010 onwards, in view of complications including heart disease (sometimes fatal), stroke, bone fractures, eye damage and hepatotoxicity. In 2007, a report by the US Senate's Finance Committee accused the company of knowing about the drug's risks well before the information became public. The same Committee pointed to evidence of efforts made by the firm from 1999 onwards to intimidate a scientist who suggested that Avandia\(^R\) could lead to cardiac disorders. Though the scientific evidence regarding the risks posed by the drug was not entirely consistent and the firm maintained that it was safe, it was reported as of July 2010 to have agreed to financial settlements of claims brought by 11,500 claimants on the grounds of injury.\(^{55}\)

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According to a report from the US Department of Justice issued in 2012, GlaxoSmithKline failed to make available two studies in which its drug Paxil\textsuperscript{R} failed to demonstrate efficacy in treating depression in patients aged under 18.\textsuperscript{56}

Though the industry has as a whole gone along with the requirement to submit all pre-marketing evidence to the regulatory authorities, it has generally demanded that the latter regard the data as confidential, not releasing it for academic or public scrutiny, since this might benefit competitors, including generic producers. Agencies have generally respected this view. When, under academic pressure,\textsuperscript{57} the European Medicines Agency decided, as of 2011, to release all information on clinical trials submitted to it by applicants, it encountered strong opposition from various companies.\textsuperscript{58} It may be some time before a definitive solution emerges, but it appears likely that much more data will in the future be released from regulatory files than has hitherto been the case.

1.7 NEW KNOWLEDGE: MANAGEMENT AND MISMANAGEMENT

Once marketed, a medicine is likely to be used in a far larger population than that involved in pre-marketing investigations; that population of users is also bound to be more diverse in terms of age, nutrition, genetic constitution, state of health and co-medication than the study group. According to one American study, more than 10 per cent of drugs approved for sale by the Food and Drug Administration have serious side effects that are not discovered on initial testing up to the time of marketing, and some of the discoveries are made very late.\textsuperscript{59} To take an extreme case: serious evidence that the use of Aspirin (acetylsalicylic acid) in children with fever could induce Reye’s syndrome only emerged

\textsuperscript{56} Cited by Kennerly MS (2012), ‘The Big Pharma business model: deception and bribery’, Internet release, 9 July.
after the drug had been in widespread use for some 80 years. In other instances a problem emerges progressively during the initial years after introduction and the evidence may be genuinely disputed for some time before a conclusion is reached and action taken; this was the case when the appetite depressant fenfluramine was found to be causing damage to the cardiac valves as well as inducing pulmonary hypertension, and was ultimately withdrawn for these reasons. The fact that this evidence of a possible harmful effect exerted by a drug commonly emerges in an irregular and uncertain manner over a long period means that it is often difficult to recognize any clear point in time at which a duty arises to warn, inform or take remedial action. There is likely to be a period of doubt and contradiction, and some suspicions may ultimately be dispelled. A firm must however at least remain aware of what is happening in the field and react in a responsible manner. Any suspicion of risk, whether arising early or late in the career of a medicine, gives rise to this duty of alertness. Depending on the nature of the evidence and the severity of the possible complication, there may at this point be at least a moral duty to look for further information, to conduct further studies, to seek impartial expert advice, and/or to consult with the authorities.

Typical of the serious doubts that can arise in the medical community when an innovative product appears to exhibit unwanted effects that were not described prior to marketing is a recent dispute regarding the Medtronic product Infuse®. This spinal bone growth-promoting product contains recombinant human bone morphogenetic protein (rhBMP-2) and became widely used in the United States and elsewhere as an adjunct to spinal surgery. At the time of approval, clinical work sponsored by the manufacturer concluded that it was free of serious side effects, but independent observations following marketing concluded that it could induce male sterility; and possibly promote tumour growth and infection. In August 2013 an Arizona court was dealing with a lawsuit brought by a patient who alleged that, as a result of treatment with Infuse, she had suffered injury since uncontrolled bone growth had occurred around the site of administration. The US Senate Finance Committee was in the meantime investigating reports that the original investigators who

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claimed that the product was safe had close ties to the company and had received large payments sometimes amounting to millions of dollars.\textsuperscript{63-64}

In the classic case of thalidomide summarized in Section 1.3, post-marketing reports of neurotoxicity and of phocomelia could and should have been taken with the utmost seriousness, whereas in fact the manufacturer set out to discredit the unfavourable (and commercially inconvenient) reports from the field. Physicians pointing to instances of suspected neurotoxicity or injury to the foetus found themselves criticized, ridiculed and even exposed to threats, including hints of legal action. Both types of adverse effect were denied until the evidence of injury became overwhelming.\textsuperscript{65} In the similarly classic case, discussed in Section 1.9, of clioquinol, marketed worldwide as an antidiarrhoeal agent since the early thirties, the Swiss manufacturer must have been aware of the inadequacy of the outdated and largely anecdotal evidence of the drug’s supposed efficacy. Highly persuasive data from the field pointed to its ability to induce subacute myelo-opticoneuropathy, proceeding to blindness and paralyses; the firm nevertheless continued for several years to market it in a number of countries where it had not been expressly forbidden.\textsuperscript{66}

Unhappily, examples of similarly injudicious behaviour have continued to emerge in much more recent years. The case of the anti-inflammatory drug rofecoxib (Vioxx\textsuperscript{R}), to which we shall return in various chapters, is particularly striking. In 2009 an independent study of the unpublished investigations that had been undertaken by Merck concluded that the firm had at least from 2001 onwards possessed evidence of a marked increase in heart attacks and strokes among rofecoxib users,\textsuperscript{67-68} yet it continued to market the drug for a further three years. The award by a Texas jury in 2005 of no less than $253 million to the widow of a man who had suffered a fatal heart attack after taking Vioxx\textsuperscript{R}\textsuperscript{69} was only the prelude to

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\textsuperscript{63} Reppeport, ‘Medtronic under fire over spinal bone product’, op. cit.
\textsuperscript{64} Lamb T (2013), ‘Infuse bone graft: Medtronic funded studies essentially ignored serious medical complications’, DrugInjuryWatch.com, 13 May.
\textsuperscript{66} See also Section 1.10.
\end{flushleft}
a massive series of claims against the company. The manufacturer’s duty to remain alert to evidence of risk was explicitly considered in legal proceedings in Australia brought against the Merck companies in this connection.  

In June 2012, the United Kingdom’s Medicines and Healthcare Products Regulatory Agency stated that the Swiss-owned Roche group had failed to inform regulators of reports of illness and death in as many as 80,000 US patients who had received certain of the group’s medicines over the previous 15 years. As reported in the media: “The reports – which included 15,161 deaths of US patients – related to the full range of drugs provided by Genentech”, a Roche subsidiary in the United States. These products were distributed by its “patient support programme” through which it offered its products to patients who were uninsured or underinsured. There were other failings identified by regulators with data on suspected side effects in 23,000 other patients and 600 participants in clinical trials. Sir Kent Woods, chief executive of the regulator, said: “Roche’s actions are unacceptable and our investigation has identified that Roche’s reporting systems are inadequate”. The Swiss company said: “Roche acknowledges it did not fully comply with regulations and appreciates the concerns that can be caused by this issue for people using its products”. Roche admitted that the data on side effects and other reports of patient health collected by the outside contractor it used to run its support programme had neither been entered into its own database nor passed on to either US or European regulators. “This was definitely unintentional”, the company added. The European Medicines Agency carried out a similar investigation into reports that Roche had apparently failed to assess.

In many countries, reports of suspected adverse effects observed in practice are submitted directly to the regulatory agencies or to bodies associated with them, or directly to the journals; in the United States,

74 Hirschler, ‘Update 3-EU raps Roche over lax drug-safety reporting’, op. cit.
However, it is customary for unpublished reports from physicians to be lodged initially with the firm concerned which is then supposed to pass them to the Food and Drug Administration. This latter procedure clearly presents an opportunity for a company to modify or suppress unfavourable reports should it choose to do so.\textsuperscript{75}

In a civil case heard in Georgia in the United States in 1998, where the link between a drug and a serious adverse effect was crucial in deciding claims for injury, the Swiss-owned defendant company asserted in the light of the literature and of adverse reaction reports lodged with the FDA that the association was insufficiently proven. The discovery process undertaken in the defendant’s American archives made it abundantly clear, however, that the firm had been in possession of a considerable number of additional physician reports that pointed to an association which it had, in direct breach of its legal obligations, failed to pass on to the Food and Drug Administration. In some instances the reports had been discarded as “incomplete” or “invalid” because certain secondary data (e.g. patient’s race or occupation) were lacking, while in other cases the reports were simply labelled “unclear” or “puzzling” and similarly set aside. The bulk of these cases were, in the view of an expert assessor, either usable as they stood or such that they could and should easily have been validated by a simple telephone call.\textsuperscript{76}

One further example relates to the cholesterol-lowering drug Baycol\textsuperscript{R} (Lipobay, cerivastatin) that was withdrawn in 2001. In the United States, the product was “voluntarily” removed from the market by the Bayer company but at the request of the FDA. Baycol was the sixth in a series of cholesterol-reducing drugs known as the statins, marketed by various firms. Since Baycol proved less effective than other statins in the dose originally approved by the FDA in 1997, the agency three years later approved an increase in the dosage. Particularly at the new dosage level, the drug proved to be substantially more likely than its congeners to induce the muscular disorder rhabdomyolysis to a degree that could

\textsuperscript{75} The \textit{International Herald Tribune} reported on 16 May 2000 that a Federal grand jury was looking into the question of whether American Home Products had hidden from the US Food and Drug Administration early reports submitted to it that its appetite suppressants Pondimin (fenfluramine) and Redux were causing potentially fatal side effects in users; these effects were later confirmed. In 2001 the first of a series of claimants were in the first instance awarded a total of $56 million in punitive and actual damages against the firm. \textit{Lopez v. American Home Products Corp.} (1981), 79th District Court, Jim Wells County.

\textsuperscript{76} Dukes MNG (1998), ‘Notes taken as an expert witness; subject to confidentiality requirements’ (unpublished).
prove fatal. By the time that the product was withdrawn, at least 52 deaths had been attributed to its use. In the course of subsequent litigation brought against the firm or its licensees by more than 10,000 patients, it was noted that the firm had itself filed with the authorities data on some 100 deaths and 1,600 injuries worldwide. In 2011 the Supreme Court of the United States accepted a class action. Though judgments differed, Bayer was reported to have paid more than $1,000 million to settle claims from patients.\textsuperscript{77,78,79} In Argentina, the Appeal Court of Buenos Aires found that Bayer had provided neither doctors nor patients with appropriate information on the risks of the drug; and it ordered Bayer to pay one victim a sum of $206,000.\textsuperscript{80}

One can point to various parties which can contribute to the continuing development of knowledge where medicines are concerned. Consumer and patient organizations have commendably contributed much to the critical review of medicines on the market, encouraging and contributing to what is commonly termed pharmacovigilance. Independent medical and scientific journals, which have at times shown some reluctance to publish negative findings, have in recent years themselves tended to become more vigilant, recognizing their role in maintaining the flow of both welcome and unwelcome information.

1.7.1 Effects of Long-term Use

Many medicines are used over very long periods, sometimes throughout life. That is most likely to be the case in patients with chronic disorders calling for continuing treatment, but there are also medicines that it is tempting to use over a period of years because their use is experienced as convenient and even enjoyable; the result may be habituation and in some instances a degree of addiction. What adverse effects such long-term use may have is generally an open question. Neither the industry, the authorities nor independent investigators have been particularly willing to perform such work, which is likely to prove costly, thankless and technically difficult.

\begin{itemize}
\item \textsuperscript{77} Kolata G (2001), 'Anticholesterol drug pulled after link with 31 deaths', \textit{New York Times}, 9 August.
\item \textsuperscript{78} Petersen M and A Berenson (2003), 'Papers indicate that Bayer knew of dangers of its cholesterol drug', \textit{New York Times}, 22 February.
\item \textsuperscript{79} Zarembo A (2011), 'Report: Bayer held back on drug dangers', \textit{Los Angeles Times}, 23 November.
\item \textsuperscript{80} Press Release (2012), 'Argentina: Bayer sentenced to pay compensation', \textit{CBG Network}, 3 October.
\end{itemize}
Such studies would seem particularly necessary where there is evidence of an unexplained rise in the incidence of disorders of the elderly, such as has been suggested where senile dementia or Alzheimer's disease are concerned. Particularly in that connection one might well ask whether we know sufficient about the very long-term effects of benzodiazepine tranquillizers on brain function. These compounds, in use on a massive scale for more than half a century, primarily as tranquillizers or sleeping aids, are known to induce dependence and to produce a reversible depression of cognitive function and memory in short-term use. The question therefore not unnaturally arises as to their possible late effects on the brain when taken over a period of many years.

It has recently become known that as early as 1982 Britain's Medical Research Council called for long-term studies with the benzodiazepines; the Council's report was for unknown reasons archived with a note that it was to remain confidential until the year 2014 and no action on it was taken. The subsequent passage of Britain's Freedom of Information Act enabled London's *The Independent* newspaper to obtain access to it in 2010 and publish its findings.\(^81\) There has been widespread reaction to the disclosure, and other writers have set the Council's recommendation alongside the evidence that has emerged sporadically over many years that benzodiazepines may in the long run impair brain function.\(^82,83\) A paper from Taiwan published in 2009 following a study of 779 benzodiazepine users and a large control group concluded: "Our findings suggest that long-term use of benzodiazepines is associated with an increased risk for dementia, but the underlying mechanisms remain unclear and further investigations are needed".\(^84\) Taken alongside parallel findings from earlier work, such a conclusion is particularly disturbing, especially since no significant effort appears to have been made by the firms concerned to follow up these issues by themselves implementing long-term investigations.

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\(^81\) Lakhani N (2010), 'Drugs linked to brain damage 30 years ago', *The Independent*.

\(^82\) Lane C (2010), 'Brain damage from benzodiazepines: the troubling facts, risks, and history of minor tranquilizers', *Psychology Today*, 18 November.


One would stress that where a study of efficacy or safety is conducted at the request of a particular national regulatory agency there is clearly a moral duty on the part of the company to make the findings available to other agencies as well. According to records released by the US Food and Drug Administration, Amylin Pharmaceuticals at one point concealed from the Agency a study conducted at the request of the Canadian authorities that raised concerns about risks to the heart presented by its anti-diabetic drug ByettaR (exenatide). When the FDA discovered the existence of the study, the company hindered it from obtaining access to the data.  

Some ethical questions inevitably arise with respect to post-marketing studies, particularly as to whether public health data normally regarded as confidential should be made available to companies to facilitate access to the facts. It is arguable that such material should be accessible to regulatory agencies on request, but the issue cannot at present be regarded as settled.  

Finally, one must recognize a strict duty incumbent on a licence holder to maintain objectivity in any follow-up studies of its drug conducted after it has been licensed. Breaches of this principle relating to fraud are considered in Chapter 5.

1.8 UNETHICAL PRACTICES REGARDING STUDY PARTICIPANTS AND EXPERIMENTAL ANIMALS

Aside from those norms that must be respected if valid scientific data are to become available and accessible, there are those that relate to the interest of the trial subject, be that subject a patient, a healthy human volunteer, or a caged laboratory animal. Particularly where human studies are concerned, questions have also commonly been raised regarding the extent to which firms may have sought to benefit from the less stringent regulations on these matters which pertain in certain countries, especially in some parts of the developing world with a weak infrastructure (see Section 1.10 below).

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1.8.1 Human Studies

Standards for the conduct of clinical studies in human subjects are classically set out in the successive editions of the Declaration of Helsinki, originally issued by the World Medical Association in 1964 and repeatedly revised since that date. The Declaration, which has been described as "the stone tablet of medical research ethics", sets out ethical standards regarding the recruitment, treatment and supervision of the volunteers and patients involved, but it also makes specific reference to the fact that, as in the case of animal experiments, no study can be regarded as ethically acceptable unless it is so designed that it can produce scientifically valid results. Principles such as those laid down in the Helsinki Declaration have been increasingly adopted into national law and accepted by industrial organizations. There are however alternative documents, including those of the European Union and the Council for International Organizations of Medical Sciences, as well as a somewhat weaker document from the International Conference on Harmonization.

Among the fundamental principles considered to govern clinical research at the present day are the performance of adequate animal studies in advance to provide a fair estimate of a drug's properties (including its potential usefulness and risks), the need for each participant to consent freely to the study after having been properly informed as to the nature of the drug and its possible effects, advance approval by an ethics committee and sufficient medical supervision of participants throughout.

Additional rules apply to trial subjects who may be particularly susceptible to risk. Drug studies in children can for example only be considered acceptable where a drug has been adequately studied in adults, where it is likely to be needed in children, and where the parents

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or guardians have given their informed consent. These standards have not always been respected. In 2006, drug trials were conducted on HIV-infected children and infants in the guardianship of the New York City Agency for Children’s Services (ACS) and living at a foster care facility. Consent was provided by the ACS. Children were obliged to take an experimental medicine and some became severely ill with potentially lethal side effects. The Johns Hopkins University, which was involved as an intermediary, admitted that prior drug safety testing and the consent procedures had been inadequate. The trial, which had been in breach of both Federal and State regulations, was suspended and the supervising clinician was barred from further research on human subjects.

One even encounters from time to time experimental studies in the most susceptible of all subjects, namely undernourished children requiring treatment with oral rehydration fluids (ORF). From August 2004 onwards, 140 Peruvian babies and young children aged from 5 to 33 months, hospitalized with severe diarrhoea, were treated not with standard ORF as recommended by the World Health Organization but with an experimentally enhanced version of the fluid. This contained two synthetic human breast milk proteins produced by genetically modified (GM) rice developed by Ventria Bioscience. Two children suffered serious allergic reactions to the material and one became allergic to various foodstuffs. It was reported that previous studies had pointed to the dangers of GM rice proteins, including allergic reactions, and the proteins had not yet been approved for testing in the United States or elsewhere. A serious contravention of these standards in a developing country is cited in Section 1.10 below.

The United States FDA has several times sought to have the Helsinki Declaration amended to accord with its own views on certain matters. In particular the Agency objects to a requirement in the Declaration that effective drugs be provided to all participants at the conclusion of the study; it also defends the use of placebo comparisons even in the treatment of life-threatening conditions for which effective therapy is not available.

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93 Ibid.
Creating a medicine

available. In 2008, the US FDA published a regulatory change eliminating the requirement that clinical trials conducted outside of the US must comply with the Declaration of Helsinki. There seems little doubt that these views within the FDA, which accord closely with those expressed by US industry, have been influenced by the latter.\textsuperscript{95} It seems regrettable, at all events, that in such matters the American authorities have chosen to accept a lesser standard for the protection of trial subjects than that accepted elsewhere.\textsuperscript{96} At least it is good to observe that the US appeal courts have chosen to follow the international lead. In the Trovan\textsuperscript{R} case involving Nigerian children, discussed in Section 1.10, a majority of the US Supreme Court chose to regard certain of the ethical principles underlying these documents as having been so widely accepted across the world that they could now be regarded as universally applicable norms; the Court cited in this regard not only the specific rulemaking documents but also two general instruments of international law, namely the International Covenant on Civil and Political Rights of 1966 and the Convention on Human Rights and Biomedicine of 1997.

The clinical study of a new drug product inevitably involves some degree of risk that cannot be entirely eliminated by any degree of caution or regulation. During an early clinical trial in Britain in 2006 of the anti-asthma drug omalizumab (Xolair\textsuperscript{R}), for example, which went on to gain widespread approval on both sides of the Atlantic for its use under adequate supervision, several participants suffered near-fatal anaphylactic reactions that apparently could not have been predicted.\textsuperscript{97}

The pharmaceutical industry is not as a rule in a position to conduct human studies within its own organization, though it has done so in the past. The normal procedure today is for such studies to be carried out by an independent physician or clinic accepting responsibility for the welfare of the patient, though the company is required by law to lay down the procedures involved and to exercise a degree of supervision. Ethical issues relating to the recruitment, treatment and care of participants are principally the concern of the external investigator and of whatever regional or institutional ethics committee may be involved. The


\textsuperscript{97} Lafolie P (2006), ‘Why has the drug trial at Northwick Park Hospital turned out to be a disaster?’ (in Swedish), \textit{Läkartidningar}, \textbf{103}, 15–16.
company sponsoring the investigation will however be in a position to exert considerable influence on events; this is the case from the very outset, when the decision of the investigator or committee to conduct the study at all will be dependent on the company's providing both a truthful and complete documentation on the drug and its known or suspected properties.

In January 2012 GlaxoSmithKline Argentina Laboratories was fined 400,000 pesos, following a report issued by the National Administration of Medicine, Food and Technology, for the killing of 14 babies during illegal trials of an anti-pneumococcal vaccine conducted between 2007 and 2008. GSK set a protocol and recruited doctors in a number of centres to employ it. These doctors took advantage of many illiterate parents who had taken their children for treatment by pressuring them into signing 28-page consent forms and getting them involved in the trials.\(^{98}\)

Quite apart from the issue of seeking the informed consent of participants, sponsors or investigators must themselves have a responsible attitude as to whether the degree and nature of risk likely to be involved in a clinical experiment are defensible or not. A participant, however intelligent and fully informed, cannot always reach a decision on this question that is fair to himself or herself.

Although instances of unethical treatment continue to occur, it would seem that major pharmaceutical companies have been cautious in this field, at least when conducting trials in industrialized countries where investigative journalists and critical health professionals are likely to detect and publicize improper practices.

Human studies in developing countries and vulnerable populations are considered in Section 1.10.3 below.

### 1.8.2 Prisoners

Prison populations have over a long period been used as a source of experimental subjects in the early stages of human studies requiring the use of healthy volunteers.\(^{99}\) Prisoners have also been used as trial subjects in certain therapeutic investigations. These practices have been most prominent in the United States; experimentation on prisoners has

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\(^{98}\) Anon. (2012), 'GSK lab fined over vaccine tests that killed 14 babies', *Buenos Aires Herald*, 4 January, as cited by herefusers.com/refusers-newsroom.

been regarded as unacceptable in principle in most other countries, though evidence from closed societies is almost completely lacking.

The advantages of performing experiments on prison populations have been explained and vigorously defended by those concerned. Prisoners are likely to be available for long periods, are kept under standard conditions with strict supervision and are not exposed to external influences. They have sometimes been recruited for very small rewards, sometimes amounting to no more than gifts of cigarettes; it has indeed not been unknown for a drug company to maintain its own testing unit within a prison. In a book published in 1973, Jessica Mitford quoted a statement made to her by one researcher that prisoners were "... fine experimental material ... and much cheaper than chimpanzees". The latter was not a mere figure of speech; a later report from the Institute for Laboratory Animal Research pointed to the increasing difficulty of obtaining non-human primates for research purposes.

Such factors led in the United States to an increasing interest in prison studies over a long period. As early as 1942, American prisoners in state penal systems had been involved in a series of dangerous medical experiments, including injections of blood from beef cattle as a possible new source of plasma, studies with atropine analogues and experiments with sleeping sickness, sand fly fever and dengue fever. The principle of experimenting on prisoners was in due course condemned at the Nuremberg trials of Nazi concentration camp physicians. The pharmaceutical industry went on to make extensive use of the option and in the United States it was estimated that by the early 1970s approximately 90 per cent of all pharmaceutical research in healthy subjects was being conducted on prisoners. That estimate is unconfirmed and it presumably relates to the proportion of all new drugs that had in part been studied on prisoners.

Between 1962 and 1966, 33 pharmaceutical companies had tested 153 experimental drugs at Holmesburg Prison in Philadelphia, including a

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103 Hornblum AM (1997), 'They were cheap and available: prisoners as research subjects in twentieth century America', *Brit. Med. J.*, 315, 1437–41.
study by the dermatologist Albert Kligman of Retin-A (tretinoin) in which researchers did not seek informed consent and prisoners were not adequately treated for pain. At one stage, Kligman was paid $10,000 by Dow Chemical to test the effect of dioxin, a component of Agent Orange, on prisoners’ skin.\textsuperscript{105,106} Hornblum reported serious complications that had occurred in Southern US prisons:

The rush to acquire prison testing sites, combined with a relaxed ethical atmosphere and little governmental oversight, provided a financial opportunity for some opportunistic physicians, while at the same time jeopardizing the health of the unsophisticated test subjects. One of the best examples of this unfortunate but all too common scenario was the controversial career of Dr Austin Stough. Claimed to have grossed close to $1 million a year, Stough – and the pharmaceutical companies he worked for – profited handsomely, while the inmates he used were made ill and some even died in an extended series of drug tests and blood plasma projects in Oklahoma, Arkansas, and Alabama.\textsuperscript{107}

There seems to be no doubt that after this time there was a marked decline in industry-sponsored studies in American prisoners, largely reflecting the public concern at revelations of the worst practices. The decline in prison studies also resulted from new regulations. The problems associated with such investigations had been considered critically at the Kennedy Hearings held by the US Senate’s Subcommittee on Health in 1975\textsuperscript{108} and became the subject of widespread debate. Legislation to restrict experiments on prison populations had been introduced by 1974\textsuperscript{109} and in 1976 the government took steps to prohibit entirely the use of Federal prisoners in medical experiments. In 1991 these provisions provided the starting point for a Federal Policy for the Protection of Human Subjects which became known as the Common Rule. The Common Rule applies to research funded by a series of Federal agencies, while the Food and Drug Administration has similar regulations for

\textsuperscript{105} Hornblum, ‘They were cheap and available: prisoners as research subjects in twentieth century America’, op. cit.
\textsuperscript{107} Hornblum, ‘They were cheap and available: prisoners as research subjects in twentieth century America’, op. cit., p. 1440.
\textsuperscript{109} US House of Representatives: HR 16160, 93rd Congress, 2nd session, 29 July 1974.
research involving the products which it regulates and thus extends to drug research. These still provide for studies in prisoners but only if the experiment poses no more than "minimal" risks to the subjects. 110

Not surprisingly, some parties claimed that the new standards were confusing or excessively restrictive, and at the request of the Department of Health and Human Services the Institute of Medicine (IOM) therefore reconsidered the applicable principles in a report published in 2006. 111 This seeks to strike a balance between the reasonable need to conduct some types of research on accessible and stable populations and the obvious possibility of risk and abuse. The IOM report in fact can be seen as favouring for the future a partial return to prison studies, given adequate safeguards. Not surprisingly, such attempts to revive the popularity of prison studies have been vigorously criticized for all the reasons noted above. 112

Concern in America and elsewhere regarding prison trials has related largely to doubts as to whether one can, in such a population, obtain genuine informed consent, uninfluenced by any form of coercion. 113 A legal review of one drug trial has noted that some prisoners did not understand parts of the study; one prisoner was receiving placebo treatment without understanding the meaning of the term. 114 Coercion may involve threats or sanctions, or prisoners may simply be exposed to financial or material temptations in order to encourage them to participate in studies. Reiter, considering an investigation in HIV-positive subjects conducted on prisoners by the University of Miami, has noted that, while they were not paid, "... they did receive better housing (with air conditioning), (and) new clothing (including more comfortable tennis shoes) ..." 115 Other commentators have questioned whether the participants in a clinical trial under these conditions can be assured of adequate medical supervision and general health care.

115 Reiter (2009), ‘Experimentation on prisoners: persistent dilemmas in rights and regulations’, op. cit., p. 525.
Finally, prisoners (and even defendants not yet sentenced) may be exposed to experimental compounds that have not undergone any form of official review. In 2006 and again in 2008, the Hythian drug company contracted with at least five different US states to enrol criminal defendants in an experimental programme on the treatment of drug addiction. State judges "diverted" defendants who had been found to possess drugs into an experimental treatment programme known as Prometa. The programme involved 30 days of treatment with three different drugs, none of which had been approved for this purpose by the FDA.

Questions also remain as to the extent to which indefensible trials on prisoners may continue in some other parts of the world, and the use for experimental purposes of other types of institutionalized populations (for example the inmates of mental hospitals or homes for the elderly). The US provisions under the Common Rule do provide added protection for other vulnerable populations (pregnant women, foetuses, neonates and children), but they do not appear to protect institutionalized groups other than prisoners.

1.8.3 Animal Studies

The conduct of animal studies is governed by principles designed to ensure that any such work is capable of delivering valid results and that no avoidable or excessive suffering is involved. For well over a century, the development of medicines has relied heavily on the performance of animal studies on a large scale before any decision is taken to examine a medicine in human subjects. Those involved in the performance of these studies argue that they are as a rule irreplaceable; early tests are designed to determine whether a compound possesses any useful degree of activity; subsequent work on a promising substance can estimate its potency and thereafter its toxicity can be assessed in acute, subacute and chronic experiments; special studies are selected to measure the compound's effect in particular conditions or on individual organ systems.

The groups that on ethical and humanitarian grounds oppose animal experiments point to the many occasions on which the evidence from such studies turns out to be only partly relevant to human beings and sometimes entirely misleading. They point to the need to devise non-animal test systems, though acknowledging the difficulties involved. Manufacturers and contract laboratories carrying out toxicity studies have sometimes been the subjects of violent protests and demonstrations. Particular anger has been expressed where animal studies are employed in the development of non-essential items such as cosmetics.
Ethical standards have been laid down at some points by industry and also in national legislation. A law passed in the Netherlands in 1997 represents a typical attempt to reach the best compromise possible in the present state of knowledge. Like similar legislation and codes adopted in some other countries, it creates a licensing system; animal experiments may be conducted only by a qualified licensee and only where they can be considered important in health research. No animal experiment shall be conducted for a purpose which, by expert consensus, may also be achieved by other means or by performing an experiment using fewer animals or entailing less distress than the experiment in question; it is further decreed that no animal experiment shall be carried out the importance of which does not justify the distress caused to the animal. Other provisions concern the need to anaesthetize the animals in certain cases, the creation of an inspectorate and the role of ethical committees. Such principles are now complemented by guidelines from other bodies, such as the "Guidelines for Ethical Conduct in the Care and Use of Nonhuman Animals in Research" issued by the American Psychological Association which came into force in 2012.

Movements devoted to the protection of animal rights have been active in alleging gross abuses of such standards within certain pharmaceutical firms. The US group SAEN (Stop Animal Exploitation Now!) has included Merck among the worst violators of US laws. The Executive Director of SAEN, Michael Budkie, has been quoted as saying that "Drug and testing companies are violating federal law on a regular basis

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117 Netherlands (1997), 'Wet op de dierproeven' (The Experiments on Animals Act (in Dutch)), Entry into force, 5 February. Available at http://www.abpi.org.uk/.
120 APsA (2011), Guidelines for Ethical Conduct in the Care and Use of Nonhuman Animals in Research, Washington, DC: American Psychological Association, Ethics Office.
and endangering the health of the American People as a result. It should surprise no one that drugs like Vioxx came out of the Merck Corporation, where federal law is broken almost every month.” According to the same source, Merck amassed eight violations in a nine-month monitoring period, while an additional ten violations of standards set by the Institutional Animal Care and Use Committee (IACUC) occurred in the three following months. One infraction involved allegedly “illegal surgery”, where holes were drilled into an animal’s skull and penetrated the brain.122

It may be noted that cases in which unfavourable evidence obtained in animal experiments is concealed or destroyed, in breach of regulatory requirements (see for example cases cited in Section 1.6. above), may now constitute a double contravention of accepted standards since the animals concerned will have suffered to no useful purpose.

1.9 MISDIRECTION OF RESEARCH

1.9.1 Profitable and Unprofitable Fields

Since the bulk of pharmaceutical research is conducted by commercial companies, essentially operating in the interests of their shareholders, it is understandable that investigations are primarily targeted on fields in which there is a good prospect of profit, such as the treatment of obesity or depression in western society. It is however regrettable that as a result relatively little investment is devoted to rare illnesses or to diseases suffered mainly in areas of poverty in the developing world (see Section 1.10). Although this poses serious problems for health care and for society as a whole, no illegality is involved in it. Various approaches have been developed to correct this imbalance. They include the development in both Europe and the United States of idealistic non-profit research centres designed to complement the activities of the commercial industry123 and new approaches to rewarding pharmaceutical innovation.124 In Part III, we turn to these approaches as productive alternatives to

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criminalization in seeking to enhance the ethical purpose and performance of the pharmaceutical industry.

1.9.2 Neglect of Older Drugs

Society has experienced difficulty in dealing adequately with the situation of the many older drugs that were developed and marketed before the advent of modern pharmaceutical regulation. Many of these were never investigated adequately to determine their efficacy and safety. Many more have simply been superseded and have vanished from the market. Others retain a substantial share of the market though their producers have generally been reluctant to invest in new studies of their efficacy and safety even when serious doubts as to their merits arise. A typical case is that of noramidopyrine, which has remained on sale in much of the world as a simple analgesic of European origin despite the fact that it can produce blood disorders in a minority of cases; it has been argued that there is no sound reason why it should continue to be available when similarly effective products for the relief of mild pain are free of these unwanted effects.\(^{125}\) The only excuse for the continued existence of such products is their comfortable profitability for the originator. Produced at negligible cost, they may continue to freewheel in the market for many years demanding nothing in the way of promotional investment, yet producing reliable income. When serious doubts arise as to their value or safety, firm regulatory action may be required to put an end to their careers.

The case of clioquinol illustrates the issue. Clioquinol was developed at the beginning of the twentieth century by the predecessors of CIBA, Basel, as an antiseptic for use on the skin. In or about 1930, after some data had suggested that the drug might well be an effective intestinal disinfectant when taken in tablet form, it was introduced as Entero-Vioform\(^{R}\), primarily for use in acute diarrhoea. It became very widely used to prevent or treat "tourist diarrhoea", although no properly designed studies appear to have been undertaken to confirm its usefulness. A typical element in supposed evidence of efficacy proved to be a testimonial provided to the manufacturer by a football team that had used the drug while travelling internationally. Progressively, however, evidence


of risk emerged. In 1935, two papers published in Spanish in Argentina described three patients who developed neurological complications while using clioquinol; the findings could hardly have been overlooked by the manufacturer, to whom they were reported. Later reports concerned neurological complications in five species of animals. From 1965 onwards veterinary practitioners reported convulsions and psychic disorders in cats and dogs given therapeutic doses. In Japan, where many persons apparently made repeated use of the drug, an increasing number of reports appeared from 1955 onwards of a neurological syndrome appearing in users, sometimes with encephalopathy or disorders of the optic nerve. In 1964 a scientific meeting termed the condition subacute myelo-optic neuropathy. An important element in proving a causal connection lay in the finding of a clioquinol chelate in the urine of affected patients. The number of Japanese cases rose rapidly, 1,452 new cases being described in 1967 alone. Curiously, some patients appeared to develop chronic intestinal disturbances as a consequence of using this supposedly anti-diarrhoeal agent. In 1979 the Tokyo District Court, passing judgment in one of a series of cases brought by patients, found the companies selling clioquinol tablets in Japan liable for damages, and a series of settlements for large sums were subsequently agreed. Three other Japanese courts passed similar judgments. Various points in the Tokyo judgment regarding corporate liability related to the foreseeability of the risk, at the latest by 1956, the company's failure to provide adequate warnings and its failure to perform toxicity tests after suspicions of injury had arisen.

It may be noted that none of the companies selling clioquinol products worldwide ever appear to have admitted fault as regards the long-term failure to conduct adequate studies of the drug's efficacy/safety balance, though the Tokyo defendants (who included Ciba-Geigy Japan Ltd) did during the trial admit that there was a causal association between the drug and SMON.

Despite the judgment, and constant pressure from WHO to terminate sales, the principal manufacturer appears to have continued production and sale up to the mid-1980s, and retailers in some countries were found to be selling clioquinol tablets as late as 1990.126

As Hansson has commented, perhaps over-cautiously, on the situation arising after the unfavourable risk/benefit ratio of the drug had been

demonstrated: “It is quite regrettable that Ciba ... did not take any particular measures of precaution as to the use of the drug in human beings ... A considerable portion of (the) SMON disaster in Japan could have been prevented if Ciba had taken appropriate measures ...”\textsuperscript{127}

One might add that in the middle of the twentieth century it was entirely feasible to develop a truly effective drug to relieve diarrhoea, and that such products were being marketed. Had Ciba had the interests of public health at heart, it could have replaced clioquinol by an alternative that was truly effective and safer.

A second case in which there was a failure on the part of manufacturers to examine either the efficacy or safety of an old drug concerned DES (diethylstilbestrol). Developed prior to 1940 as a non-steroidal (and therefore low-cost) oestrogen, DES came into very widespread use on the basis of an (unproven) academic theory that habitual abortion was a consequence of oestrogen deficiency, and that the administration of an oestrogen during pregnancy would therefore improve the chances of its proceeding to term. Only some 35 years later did it become clear that the use of DES could lead to serious complications, including malignancies, in the mother and the offspring, perhaps even affecting the third generation. Around 1975 the drug was for this reason withdrawn. The drug had never been patented and was therefore manufactured by a series of different companies. In the Netherlands, where DES had been very extensively used, a series of claims were lodged against the producers. Since it was generally impossible to determine which manufacturer’s product had been used by a particular claimant, all the firms involved agreed to contribute to a compensation fund.\textsuperscript{128}

As noted in Section 1.7 above, companies have also failed to study the long-term effects of drugs such as the benzodiazepines which are likely to be taken over very long periods. These and similar histories point to the failure of pharmaceutical companies to take seriously the fact that they remain responsible for the effects – wanted and unwanted – of their products so long as they remain on the market.

\textsuperscript{127} Hansson O (1979), \textit{Arzneimittel-Multis und der SMON-Skandal} (in German; remarks cited above are in English), Berlin: Arzneimittel-Informations-Dienst Gmbh.

RESEARCH AND DEVELOPING COUNTRIES

Drugs for Tropical Diseases

The industry’s lack of motivation and interest as regards the creation of drugs that will serve to meet the needs of small populations or areas with little purchasing power has been touched on in Section 1.9. When one considers the paucity of research devoted to relieving the specific health problems of the developing world, and sets it alongside the marketing activities of the industry in the same countries (and the sums expended on diseases of prosperity in the western world), it is hard not to condemn and search for reforms. As a senior member of the staff of Médicins sans Frontières put it in 2008:

Every day, medical staff members of Médicins sans Frontières (MSF) witness first hand the failure of a market-driven pharmaceutical system which caters to those who can pay large sums for their drugs, but leaves those who can’t out in the dark. Tuberculosis is the poster child for these failures, where the newest drugs available were developed in the 1960s, and the most commonly used method to diagnose this curable disease – which continues to kill 1.7 million people each year – was developed nearly 130 years ago. Changing the rules of the game will mean separating the cost of research and development from the price of products.129

The problem was presented in detail in a major report by MSF published in 2001.130 Another paper in that year131 concluded that of 1,233 new chemical entities found between 1975 and 1997 to have useful pharmacological properties only 13 were for the treatment of diseases predominantly present in poor countries. While HIV/AIDS, tuberculosis and malaria have progressively received more funding than in the past because of their global significance, many other conditions affecting poor populations remain neglected. In many instances some form of treatment does exist, but the drugs used are prohibitively expensive or toxic. In Part III we consider the policy option of a responsive pyramid of supports to strengthen the capability of the industry to be more responsive to the

131 Byström M and P Einarsson (2001), TRIPS: Consequences for Developing Countries, Stockholm: SIDA.
diseases of poor countries. Such a pyramid will include various kinds of prizes and other incentives for finding solutions.

1.10.2 Clinical Studies in Developing Countries and Vulnerable Populations

Up to this point we have considered the basic standards in drug research that, in the interests of society, should hold good everywhere. Most of those standards, however, have grown up in industrialized countries. When one turns to consider the less industrialized or developing world, one is faced right away with additional problems that call for a solution. Certain of those challenges arise because legal systems in some of these countries tend to be less well developed or frankly dysfunctional. Part III considers options for networked governance of safety and efficacy that empowers wider networks of actors beyond developing country regulators, including transnational actors, to compensate for some of the capacity deficits of weak states. Other challenges reflect the need to take account of lower standards of education or levels of literacy. There can be perfectly valid reasons to perform certain studies with drugs in the developing world, for example where it is possible that the effects of a drug may be influenced by the climate, by diet, racial factors or by body weight; again, a medicine that is specifically likely to be of value in tropical diseases will have to be evaluated in those parts of the world where these diseases are common. It has also been noted, with respect to Latin America, that the population is “coveted by the companies because their bodies have not been adulterated by other drugs that might interfere with the effects of an experimental treatment”. If human studies are to be carried out in such an environment, the best international standards must be strictly respected. What one must not do is locate clinical research in the developing world as a means of evading rules or cutting corners. The fact that the costs and regulatory obstacles may be relatively less in the developing world is no valid reason for lowering the standards of investigation, ethics or patient care. Too often, such things have happened.

A survey published in 2004 concluded that a quarter of the clinical trials carried out in developing countries do not undergo any form of ethical review in the host nation and similar findings have been

reported by others.\textsuperscript{134} For any body proposing to conduct trials involving risk it may well be tempting to undertake these in a developing country. Certainly during work in developing countries one not infrequently encounters reports of ethical and technical shortcomings in clinical investigations sponsored in their populations by western pharmaceutical companies, but only in a few instances have they been the subject of widely reported litigation. Particular problems, both with the trials themselves and with claiming compensation for injury, are posed by limited education or literacy, and there may be problems with language as well; if anything, trial subjects in developing countries have a need for a greater degree of protection than those in the West. A Pfizer case may be cited as an example of a multinational firm alleged to have breached basic ethical and legal standards in this regard. A large number of Nigerian families brought a civil case in the US courts against Pfizer; all related to a clinical study of the experimental antibiotic trovafloxacin (Trovan\textsuperscript{R}) initiated by Pfizer in 1996 in Nigerian children during a severe epidemic of bacterial meningitis.\textsuperscript{135} The intention was to obtain clinical efficacy data that could be used to support new drug applications in the USA and elsewhere. According to claimants, Pfizer had acted illegally since, among other things:

1. The trial had not been approved by the Nigerian authorities (a letter of approval that subsequently came to light was admitted by an official witness to have been written later by him and antedated).
2. No informed consent to participation by the children had been obtained from their parents or guardians.
3. Pfizer knew that trovafloxacin had never previously been tested on children in the form being used in this study.
4. Animal tests had shown that trovafloxacin had life-threatening side effects, including liver damage.
5. The parents were not told of the possible risks involved nor informed of their right to the proven treatment that the organization Médecins sans Frontières (MSF) was already providing free of charge at the same site.


6. Although a control group was to receive a recognized antibiotic for comparative purposes, the comparator substance was to be administered in a low dose, apparently to suggest the superiority of trovafloxacin.

7. After some two weeks, Pfizer allegedly concluded the experiment and left without administering follow-up care.

Again according to the claimants, the tests, conducted on 200 children, caused the deaths of 11 children, five of whom had taken TrovanR and six of whom had taken the lowered dose of cefatrioxone, while many others were left blind, deaf, paralysed, or brain-damaged. It may be noted that, in 1998, the United States FDA approved TrovanR for use on adult patients only, but that its use was later restricted because of liver damage. The injuries suffered were the subject of the litigation brought against the Pfizer Corporation in Nigeria and the United States. The firm agreed to a settlement involving a total payment of $75 million, equivalent to $175,000 for each victim, and undertook to settle a series of miscellaneous claims.136 As of October 2011, however, 15 years after the event in question, the press reported that only a small proportion of the total sum agreed appeared to have been disbursed.137

A particular question that arises when an experimental medicine is tested in a developing country is whether, in patients who require active treatment and must not be exposed to placebo, the test drug should be compared with the best existing therapy or with whatever medicine these individuals would normally receive in their own situation (which may be far from ideal).138 Again, once the study is completed, should a participant be transferred to optimal therapy or to whatever is available locally? While the answer may depend upon the total situation, the basic principle is that the individual subject's health and welfare must not be adversely affected by participation in the study.

In some instances healthy participants in clinical trials in developing countries are in fact disadvantaged individuals whose situation puts them under duress to participate as a means of earning some income. In India, where local contract research organizations maintain panels of potential participants for trials sponsored by multinational companies, many of the

136 Stephens J (2009), 'Pfizer to pay $75 million to settle Trovan-testing suit', Washington Post, 31 July.
persons listed on a panel created by the Wellquest Company were for example reported to be unemployed textile workers.\textsuperscript{139}

Again, one repeatedly encounters reports of clinical studies performed in developing countries which have been undertaken without awaiting the outcome of preliminary investigations in animals or which in other respects breach the standards set by the Helsinki Declaration.\textsuperscript{140} In India, multi-centre Phase III clinical trials of the diabetes drug ragaglitazar by Novo Nordisk were suspended when urinary bladder tumours were found in studies on rats. It has been argued that the results of these studies should have been available before the clinical work was undertaken, but this has been disputed.\textsuperscript{141}

The performance of unacceptable clinical studies in India has resulted in emphatic protests.\textsuperscript{142} While the multinational involved may point out that the local contractor usually provides a comprehensive service and thus carries all responsibility for the rights and wrongs of any trial, it is clear from the available evidence on various such cases that the sponsor is often deeply involved. The Indian endocrinologist Shashank Joshi has pointed out that multinational corporations typically determine every stage of the research. In his words, "All we do is provide them with the material. They dictate every detail of the trial protocol, they deal with IEC review, they control the data analysis and publication ... The investigator is part of a master slave relationship."\textsuperscript{143} The same commentator points out that if a drug is found ineffective or even dangerous, the company can bury the findings without publishing them; if researchers try to publish themselves, they can end up in court.

The Netherlands Foundation SOMO (Centre for Research on Multinational Corporations) and India’s CSER (Centre for the Study of Ethics and Rights) are among the bodies which have in recent years published a series of reports on what are considered to be unethical studies carried

\textsuperscript{141} Maggon K (2002), ‘Risk-benefit assessment of Glitazones’, Express Pharma Pulse (India), 12 September.
\textsuperscript{143} Cited by Srinivasan S, ‘Indian guinea pigs for sale: outsourcing clinical trials’, op. cit.
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out with drugs in developing countries. A number of the reports are summarized below. GlaxoSmithKline conducted a Phase 2b trial of lapatinib monotherapy for chemotherapy naïve patients with advanced HER2 positive breast cancer at three sites in India. The majority of breast cancer patients in India cannot afford proper treatment; this trial required seriously ill patients who had not received treatment for their condition. Their economic vulnerability forces patients in India to take part in trials in order to get access to treatment and to disregard the potential risks that participating in clinical trials entails. By carrying out this clinical trial in India, GlaxoSmithKline took advantage of the vulnerable position of breast cancer patients. A statement by a representative of the company seemed to indicate that patients who stopped responding to lapatinib were not assured appropriate treatment once the trial was completed. As a concurrent phase multi-country trial conducted before January 2005, the trial also contravened an Indian government regulation that was in place when it was conducted.

In 2003 the Novartis drug letrozole (Femara®), which is widely approved for the post-menopausal treatment of mammary carcinoma but for no other indication, was tested by Sun Pharmaceuticals of India on more than 400 Indian women for its possible ability to induce ovulation. All the women had experienced difficulty in conceiving, but all were enrolled without their knowledge or consent. None was aware that she was taking part in a clinical experiment or that the drug that she was being given had nowhere been approved for this purpose.

The Boehringer-Ingelheim drug Nevirapine (Viramune®), a recognized treatment for HIV/AIDS, was in collaboration between the company and the US National Institutes of Health (NIH) tested on more than 400 Ugandan women to determine whether it might prevent mother-to-child transmission of the HIV virus. A single dose was administered at the time of delivery. Investigators failed to get patients' consent about changes in protocol during the experiment and administered incorrect doses. There were serious problems in record keeping and delays and underreporting

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145 Srinivasan S and S Nikarge (2009), Ethical concerns in Clinical Trials in India: An Investigation, Mumbai: CSER.
146 Ibid., p. 1.
of fatal and life-threatening problems. Fourteen deaths were not reported. Researchers acknowledged "thousands" of side effects, but adverse reactions were not systematically recorded. Boehringer-Ingelheim asked the NIH to destroy an early copy of the research report before audit by the US Food and Drug Administration. In fairness it should be added that the results of this study provided a basis for a means of preventing or at least reducing the risk of mother to child transmission; the trial could however have been performed without committing the ethical errors noted above.148

In or about 2008, Johnson and Johnson conducted a placebo-controlled trial in India of their drug risperidone (Risperidal®) for the treatment of acute mania. The patients who were recruited for the trial had all been receiving effective anti-mania therapy. In all cases the effective drug was withdrawn and the patients were untruthfully told that it was no longer available. A patient who was interviewed declared that he had signed a form because the doctor asked him to do so, but that he was not informed that he was to take part in a clinical trial. Critics have commented that informed consent was not consistently obtained and that it is improper and dangerous to expose a patient with acute mania to a placebo regime. Johnson and Johnson regarded both criticisms as invalid. The case provides a further reminder that genuine differences of opinion can exist as regards the acceptability of a trial or of placebo comparisons. However, SOMO points out that the investigation contravened the Indian Department of Health's rules in various respects (informed consent was not properly obtained; the use of a placebo was controversial because it was unnecessarily dangerous; it was not explained to all patients that medical care provided was linked to research).149

Maxim Pharmaceuticals sought permission from the US FDA to perform a clinical study with its histamine derivative Maxamine for possible use in hepatitis C. The FDA considered that more studies to determine the product's safety should first be performed in animals. To overcome this obstacle the firm performed its study in Russia, where permission was obtained, but it improperly failed to inform the Russian health authorities of the FDA's objection, nor was this fact mentioned when informed consent was sought from patients.150

Considerable concern has been expressed at breaches of ethics in studies conducted by multinational firms (but also by other parties) in

148 Ibid., p. 6.
149 Ibid., p. 10.
vulnerable populations in Latin America. In or about 1997 Hoechst Marion Roussel (later known as Sanofi-Aventis) undertook studies of cariporide, a selective Na+-H+ exchange inhibitor, in various countries including Argentina. The work was intended to assess the effectiveness of the compound in preventing further cardiac damage following angina pectoris, arterial cleaning or bypass surgery. Of the 137 patients participating in the trial at the Naval Hospital in Buenos Aires, none properly consented to the trial. The signatures on at least 80 informed consent forms were forged, and those participants who did sign the paper themselves did not know its contents. In total 13 patients died and at least three of them were, according to the SOMO report, considered to have died because they were not given the correct treatment. Data in medical records was changed and key documentation disappeared.

It may be noted that in recent years similar evidence has come to the fore that western companies conducted unethical studies on hospitalized patients in the former German Democratic Republic, access being obtained through massive financial payouts to the regime. The above cases represent only a small sample of the many reports which have been published during recent years on the subject of unethical studies in vulnerable subjects and populations. In the absence of adequate measures to end such abuses, such reports will no doubt continue to appear.

1.10.3 The Sale of Discredited Drugs

While the present chapter is devoted to issues of research and development it is relevant to touch briefly on the fact that in the developing world one sometimes finds medicines on sale which cannot be said to be based on any valid research at all. These are products which in the West have been discredited as being ineffective, unsafe or both. As the British Medical Journal wrote in 1997: "The sale, commonly backed by promotion, of unsafe drugs in the developing world has long attracted criticism, particularly when products have been banned or restricted in the country.
of manufacture".\textsuperscript{154} In the early 1990s one could still encounter on a street market in Pakistan glass jars filled with clioquinol for the relief of diarrhoea or with phenacetin as a headache remedy.\textsuperscript{155} Both had been removed from the market in the West at least 15 years previously – the one for inducing paralysis and blindness (see Section 1.9 above) and the other because of damage to the kidneys.\textsuperscript{156} More than a year after rofecoxib (Vioxx\textsuperscript{R}) had been withdrawn worldwide for safety reasons in 2004, it was still widely available in Delhi.\textsuperscript{157}

These examples pale into insignificance, however, when one considers the appalling renaissance of diethylene glycol as a pharmaceutical solvent in the twenty-first century. The fatal consequences of using diethylene glycol as a solvent for sulphanilamide in the United States in 1937 were recalled in Section 1.3 above. Yet in October 2006 the Ministry of Health of Panama found itself obliged to order the recall of seven medicinal products – all using diethylene glycol as a solvent – after 21 persons had died of renal failure. In due course the death toll attained at least 51. The medicines sold in Panama had been produced locally but using a solvent purchased from Spain and in fact originating in China.\textsuperscript{158} Panama was not the only country affected; diethylene glycol adulteration of glycerine in medicines had since 1992 similarly caused fatalities in India, Haiti, Argentina, Bangladesh and – not in the last place – Nigeria.\textsuperscript{159}

It is inconceivable that recurrent instances such as these could occur in the absence of gross negligence, indifference or outright deceit on the part of a supplier. Just occasionally, one can lift a corner of the veil that conceals the thinking behind such dubious manipulations. Klaus Leisinger from Switzerland, who at one time travelled the world for Ciba-Geigy to proclaim the efficacy and safety of clioquinol, admitted in later years that he had been misled: "The explanation is embarrassing but

\begin{itemize}
\item \textsuperscript{155} Lauritzen E and MNG Dukes (1994), ‘Travel report to Euro Health Group’ (unpublished).
\item \textsuperscript{157} Ksinha K (2005), ‘Vioxx’s Indian make still on sale’, \textit{Times of India}, 25 August.
\end{itemize}
really very simple”, he told Milton Silverman’s team. “Some medical people in my home office had not told me the whole truth”. We turn to other aspects of drug marketing in developing countries later in this volume (Chapter 4) and more widely to explicit fraud in both developed and developing countries (Chapter 5).

1.11 CONCLUSION

This chapter has been concerned primarily with the technical standards of studies to determine the safety and efficacy of drugs. As we have seen, the definition of standards in drug studies has in recent decades been the subject of an increasingly broad consensus in society led by the health professions and the bodies representing the public interest in drug approval. We conclude in Part III that this is a considerable asset in energizing regulatory strategies that might be effective. The pharmaceutical industry has participated in that consensus to an increasing extent, while continuing to warn of the possible adverse consequences of excessive restriction. The broadly agreed regime that reflects this consensus can however only function adequately if all parties consistently respect it. An examination of practice unfortunately suggests that on the one hand there are still those who would prefer less adequate standards, and some who succumb all too readily to the temptation to avoid conforming to rules when self-interest is more dominant and especially where the public interest is only weakly represented. The drug regulatory process as it now exists in much of the world requires above all an honest meeting of minds and complete openness on both sides if the community is to benefit to the full. It is probably true that every drug regulatory agency recognizes on the basis of experience certain pharmaceutical executives and scientists whom it can in general trust, and certain others who have not earned such trust and whose role needs to be monitored with the greatest care and a degree of healthy suspicion.

Similarly, the standards of ethics relating to the interest of trial subjects and test animals have been the subject of a high degree of consensus. In that respect society has come a long way in a generation. Here too, however, the main issue for the coming years will be to what extent sponsors and investigators indeed conform to the agreed standards, even when this may render research more complex or costly. Both a sick child

undergoing treatment in Africa and an animal in the research laboratory have the right to expect adherence to the spirit as well as to the letter of the rules that have been devised to protect them.

Some of the approaches that are called for to remedy current malpractice in these areas will be considered in the closing section of this book, but two of them justify brief mention here. One relates to the corrective role that may be played by a company’s individual shareholders, who themselves are likely to be consumers of medicines and therefore personally concerned with issues of safety and efficacy. It is striking that in a related field – that of food products – at least one consumer organization has chosen to acquire a number of shares in a manufacturing corporation in order to raise its voice at shareholder meetings. Another approach reflects the need to involve the community more directly in the work of regulatory authorities in dealing with these and other matters. Too often (but sometimes correctly) regulation has been viewed as a cosy process in which the regulators and the regulated operate in tandem to arrive at what are conceived as fair decisions, to the exclusion of the broad public on whose behalf regulation was primarily created. Surprisingly, many regulatory bodies have little or no provision for consultation with consumer bodies or independent patient organizations. It is to the credit of the European Union’s body in this field that provision has in recent years been made for such involvement, and although the independence from industry of some patient groups is open to doubt, this type of involvement is in principle desirable if the community is to develop a sufficient grip on the process of drug investigation and regulation.

Part III of the book develops some more general approaches to transparency that are relevant to consumers and shareholders alike. This chapter has also shown the importance of transparency of regulatory action in one country so it can be seen by regulators in another. In Part III we therefore develop the idea of regulators (and criminal prosecutors) acquiring a cosmopolitan ethic. This can mean that, when a Corporate Integrity Agreement is crafted following a serious breach of the law, the reach of that agreement, and the reach of the improved auditing or scientific integrity it mandates, can be agreed to apply to all countries in which the firm sells or tests medicines. More than that, we will discuss the need for the weaknesses of critical stakeholders (such as developing country regulators) to be adequately compensated for by the strengths of

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161 Anon. (1993), 'Bishop calls for changes as Nestlé shareholders are greeted by demonstration', *Baby Milk Action Update*, 11 July.
networks of other stakeholders. A web of problems, we will conclude, needs a web of networked controls in which the criminal law is just one strand.

A much wider challenge uncovered by the cases in this chapter is that of diffused accountability. We have seen that a contract laboratory or a clinician may be guilty of unethical or illegal practices. Often it is difficult to judge, and difficult for courts to ascertain, whether the pharmaceutical company that contracts this work is a victim, or whether the intention of the firm’s executives was to have corner-cutting work done outside the firm to insulate them from blame. In addition, this chapter has shown that there can be ambiguities in the law itself, in the boundary between the unethical and the illegal. The criminal law will prove to be a blunt instrument to regulate legal but unethical practices such as declining to develop products that can cure diseases of the poor because they are unprofitable. This may need a more responsive kind of capitalism than the present one, a challenge engaged in the final chapter of this book.

While we will get to remedies in Part III that are a basis for hope, there are aspects of the story of this chapter that should leave us in despair. How can it be that products that are the subject of regime-changing significance in the West, such as thalidomide, clioquinol and diethylene glycol, can still be killing people in developing countries decades later? In the case of diethylene glycol, how have we arrived in a world where a drug banned for causing 107 deaths in 1937 in the United States is sourced from China in the 1990s and 2000s to cause far greater numbers of deaths in developing countries from Nigeria to India to Panama in 2006?

One must however stress in closing that issues of safety and efficacy are not always clear-cut. From time to time, one encounters honest differences of opinion between scientists regarding the acceptability of a medicine. As of 2013 there was, for example, still disagreement regarding the safety of a modified insulin product developed by Novo Nordisk of Denmark that was claimed to offer a much improved degree of flexibility in dosage schedules. While a series of major regulatory agencies in Europe and elsewhere regarded the modified product as fully acceptable,\(^\text{162}\) the United States FDA had demanded substantial additional testing to exclude the risk of cardiovascular complications, which would at the least delay marketing by a matter of months or even

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\(^{162}\) Anon. (2013), ‘Novo Nordisk launches flexible dosing insulin named Tresiba’, Money Control.com (India), 23 September.
years.\textsuperscript{163} With academic opinion on the issue divided, there was little reason to regard Novo's introduction of the drug as improper. In such matters the truth may only emerge after a considerable time.

\textsuperscript{163} Anon. (2013), 'FDA vetoes Novo Nordisk insulin drug', Fox News.com, 13 February.
2. Safe, unsafe and improper manufacturing practices

2.1 AN ABSOLUTE STANDARD?

Many of the world’s medicines are manufactured in precisely the sort of stainless steel and glass factories that are the showpieces of modern industry, fitted out with sophisticated equipment and staffed by white-coated experts. Procedures for Good Manufacturing Practice (GMP) are laid down in fine detail, with approval and inspection by the health authorities,¹ and laboratories are to hand for checking every stage of production. In almost every respect, the standards applicable to drug manufacturing are accessible, absolute and applicable across the board. In the making of pharmaceuticals, just as in the building of aircraft, there is after all no room for error: the misplacement of a single screw when constructing a plane may lead to the death of hundreds of passengers; with medicines, which can be active in microgram quantities, the toxic dose of the active substance may be only very slightly higher than the dose used in treatment, and the slightest slip in formulation may have tragic consequences for numerous users. In one respect the pharmaceutical situation creates even more stringent demands; while an aircraft will be checked and rechecked by any conscientious operator before each flight, a medicine, once packaged in the factory, is unlikely to be examined again before it is opened and consumed by the patient; at that stage even a serious quality defect is likely to go unrecognized until disaster supervenes.

The broad agreement, in both the public and private sectors, that there is a need to maintain the very highest standards in the making of medicines is reflected in the printed standards for Good Manufacturing Practice (GMP) issued or accepted by many authorities, such as the European Commission.\(^2\)\(^3\) Any major manufacturer of medicines is likely to have laid down its own standards of GMP, and corresponding Standard Operating Procedures (SOPs) that are likely to be similar to those drawn up by the World Health Organization or the public health authorities\(^4\) and that in some cases are even more stringent. Those standards will relate among other things to the training and supervision of staff, the accommodation and equipment of the plant, the selection of materials and methods for every phase of production, the keeping of detailed records and the maintenance of rigid systems of quality assurance and control. The public health authorities for their part will ensure critical licensing and inspection according to these standards and will when necessary investigate shortcomings and call for correction. A conscientious manufacturer will also draw the attention of the authorities to a suspected product defect and suspend the sale of the item involved until the apparent fault has been corrected.\(^5\)

It is not surprising to encounter shortcomings when medicines are prepared by the sort of backstreet counterfeiters and frauds considered in Chapter 5; it is however astonishing to encounter repeated and grave instances of manufacturing fault in supposedly reputable industries. In 2000, Schering-Plough was forced to recall several million asthma inhalers, made in New Jersey, after determining that some of them may not have been properly filled with the active material (albuterol). The following year, inspectors found the same problems at the firm's plant in Puerto Rico. That same year, the FDA investigated the inhalers after Public Citizen, the Washington consumer group, obtained reports showing that some patients had died after using them.\(^6\) Other problems

\(^2\) See, for example: EC, *The rules governing medicinal products*, op. cit.

\(^3\) A listing of the most influential documents in this field has been provided by Patel KT and NP Chotai (2011), ‘Harmonized GMP requirements’, *J. Young Pharm.*, 3(2), 138-150.


\(^5\) Adams B (2012), ‘Novartis flu vaccine suspended in some EU countries’, *Pharma Times*, 30 October.

\(^6\) Peterson M (2002), ‘Schering Plough says F.D.A. investigation may focus on some of its products’, *New York Times*, 16 May.
involved the quality of the oral anti-allergy product Claritin® and lack of cleanliness in production areas. In 2002 a $500 million fine and external quality controls were imposed on the firm.7

Errors detected by the authorities sometimes continue despite punitive and other measures. Caraco Pharmaceutical Laboratories of Detroit, which repeatedly claimed that its generic pharmaceuticals offered "value with quality",8 was found, following a series of inspectorate visits, to be in error as regards both manufacturing procedures and quality control; cross-contamination between various products was also detected. The firm responded inadequately to demands for change and, in June 2009, to avoid possible risks to public health, US Marshals at the request of the FDA seized the firm's entire manufactured stock, held at three plants, as well as certain ingredients.9

Early in 2010 the United States FDA lodged a complaint with Pfizer’s Central Stability Laboratory relating to the firm’s complaint-handling system and documentation. In particular there was “no assurance that corrective actions in response to complaint trends identified” were adequately completed; in one particular instance where a product defect had been identified the incidence of the defect actually increased.10

A regulatory agency may close a manufacturing plant, in whole or in part, where a severe risk to public health is suspected. The Chiron company in Liverpool, England, specialized in biotechnological products, including the influenza vaccine Fluvirin®. In October 2004, Britain’s Medicines and Healthcare Products Regulatory Agency determined, following inspection, that the plant was not producing the vaccine according to GMP standards, and there was concern that as a result it might be contaminated with microorganisms. The manufacturing line for Fluvirin® was closed down, the relevant licence being suspended in the first instance for three months. Following a radical improvement in

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procedures, the firm later regained its licence and resumed manufacturing.\textsuperscript{11} Closure of a manufacturing plant by a regulatory agency is an extreme measure that may be adopted where a severe risk to public health is suspected, for example if an injectable product is contaminated by bacteria.

In manufacturing, as in quality control, methods need to be in line with regulations, and, where a method has been specifically approved by a regulatory agency, it must not be altered without obtaining further approval. In 1997, Copley Pharmaceutical, a generic drug manufacturer in Massachusetts, pleaded guilty to a count of conspiracy to defraud the Food and Drug Administration and agreed to pay a fine of $10.65 million. The company had been charged with changing drug manufacturing methods from those approved by the FDA, falsifying manufacturing batch records to conceal manufacturing deviations and submitting to the FDA false annual reports which did not disclose these manufacturing changes.\textsuperscript{12}

In some such cases, serious error may reflect inexperience, a degree of laxity or even a measure of indifference, but once in a while it can only be characterized as constituting criminal negligence. Even large and generally well-reputed firms sometimes have difficulty in maintaining consistently the stringent standards that drug manufacturing demands. Vaccine manufacturing in particular seems to raise problems, some of which may be detected only through inspection. In October 2007 the Merck plant at West Point, Pennsylvania detected sterility problems in its vaccines for Haemophilus influenza type B and hepatitis and 1.2 million doses were recalled. An FDA inspection between November and January found "significant objectionable conditions" in the manufacture of both vaccines and drug ingredients at the plant. The firm's response to the inspection report was considered inadequate and a warning letter followed. According to the agency, Merck staff failed to investigate thoroughly the fact that some vaccine batches had not met specifications; some combination measles-mumps-rubella shots had been distributed despite the fact that they had failed "visual inspection for critical

\textsuperscript{11} Hoffmann C (2005), 'UK regulators reinstate Chiron's Fluvirin vaccine licence', available at http://www.firstwordpharma.com/node/218627#axzz2hQfMVKRM (accessed 12 October 2013).

\textsuperscript{12} Corporate Crime Reporter (1997), \textbf{22}(1).
defects”. Nor did the plant, according to the FDA, have written procedures, tests or other laboratory controls to ensure the “identity, strength, quality and purity” of the products concerned.13

A report such as the above seems to illustrate the need for both internal and external controls on manufacturing procedures. However, it also points to the fact that the stringent standards set by an agency such as the FDA reflect the aim of achieving near perfection; products that now and then slip a little below these standards break the law but do not necessarily pose any serious risk. In this instance the FDA stated that it “does not believe that the issues identified will affect the safety of the vaccines” made at the West Point plant, in essence confirming assurances on this score advanced by the company.

A government agency detecting shortcomings in manufacturing or quality control routines in a plant that has previously adhered to recognized standards is in the first instance likely to issue a firm and detailed warning and to demand immediate correction. Early in 2010 the United States FDA lodged a complaint with Pfizer’s Central Stability Laboratory relating to the firm’s complaint-handling system, corrective actions and inadequate documentation. In particular there was “no assurance that corrective actions in response to complaint trends identified” were adequately completed; in one particular instance where a product defect had been identified, the matter was investigated by the company, but the incidence of the defect actually increased.14

If there is some reason to suspect that a quality defect might adversely affect patients, an agency may as a precaution provisionally suspend distribution of the product concerned. In 2012 the European Medicines Agency took this step with regard to DepoCyteR (cytarabine) after a joint British and French inspection team had found evidence that sterility was insufficiently ensured during production by Pacira Pharmaceuticals in California, even though there was no evidence that the final product was contaminated.15

Particularly when one sets out to apply standards developed in one country to another in a different part of the world, one may encounter

problems. Concepts regarding manufacturing routines and quality procedures do vary to some extent from one country to another. When in 2003 Pfizer acquired Sweden’s Pharmacia, a well-reputed firm that had operated for many years under the extremely watchful eye of Swedish regulators and inspectors, it hardly expected to receive the warning letter from the FDA that in due course arrived, raising 70 objections to Pharmacia’s manufacturing and control procedures. All the objections were in due course met.

In a consultancy visit to a pre-1990 factory in Albania, it was found that visual checking of ampoules for absence of particulate contamination was not carried out in front of an illuminated screen but using light from a window with a lace curtain. Factory management argued that use of an illuminated screen would prove tiring or injurious for the eyes of the workers involved.16 In some such cases it can be difficult to change engrained habits, but it must always be borne in mind that the health consequences of manufacturing defects can easily be overlooked, especially if there is little effective feedback from the field. Some serious manufacturing defects uncovered by inspection come to light not as a result of government surveillance but because a major manufacturer has itself inspected the premises of a contract producer and found fault. In July 2009 Sandoz in Britain alerted health professionals to defects that it had found in the manufacturing of three of its products that were being made under contract by a third party (MJ Biopharm in India). The faults were sufficiently serious to warrant withdrawal of all three medicines.17 They included errors in both manufacturing and quality control as well as inaccuracies contained in documents such as batch manufacturing and testing records. Medicines made for other British firms by MJ Biopharm were withdrawn at the same time.18

In the United States some hospitals and physicians reduce expenses by procuring drugs from so-called compounding centres which, under the supervision of a pharmacist, procure starting materials from generic sources and undertake the final stage of formulation themselves. In 1998 Congress decided to exempt these compounding centres from FDA manufacturing inspection, essentially aligning them in this respect with retail pharmacies; products were to be compounded exclusively against individual prescriptions. On occasion, however, a compounding centre has improperly engaged in mass production for which it was not

equipped; in late 2012 the activities of such a centre in New England were exposed by a whistleblower after it had supplied large quantities of corticosteroid injections that were contaminated with fungus, resulting in 58 deaths from meningitis and 720 other cases of fungal meningitis.\textsuperscript{19,20,21} It is only fair to point out that many firms do make extensive efforts to ensure that their products are manufactured to an acceptable standard; many maintain their own internal regulations to this end, and some companies will on occasion test the reliability of their own systems by sending a defective product down the production line to determine whether and how it is detected and stopped.

2.2 ACCOMMODATION AND EQUIPMENT

Both the manufacturer and the regulations to which it is subject must be expected to set clear standards for the building, servicing and maintenance of the premises in which pharmaceuticals are to be made. Some attempts to enter the field have been astonishingly inept. When a proposal was made in Morocco to equip a former warehouse as a government plant to prepare simple over-the-counter remedies, primarily syrups and powders, the Health Ministry requested inspection by the World Health Organization. It was found that the building lacked security, air conditioning and alarm systems, that there was no laboratory accommodation or sterilization equipment, that separate channels for arriving and departing goods and for pre-release and post-release items would have to be built, and that all internal surfaces would require covering with sealed and washable materials. Sterilizable and sealed lighting equipment would have to be installed. Within the available space there would be no possibility for two or more entirely separate production lines. Administrative and working areas would have to be separated and washing and changing facilities provided for male and female staff. Faced with these as minimum requirements it was recommended that the proposal be rejected.\textsuperscript{22}

\textsuperscript{19} AP (2012), ‘Two more drugs from meningitis-linked firm probed’, \textit{Associated Press}, 16 October.
2.3 STAFF ACCOUNTABILITY

As early as the opening years of the nineteenth century the law of France set certain manufacturing standards, ultimately introducing a requirement that at each plant a "responsible pharmacist" should head the production process. Today, requirements for the staffing of such a plant relate to training and experience at all levels, and the performance of staff is subject to inspection. Records must indicate precisely which staff member has the responsibility for particular tasks and confirm that the employee has indeed performed those tasks himself or herself (in certain cases with an additional obligation to have the matter cross-checked independently by a second individual). Where agencies have found fault with record keeping it is often precisely these matters that have been handled incorrectly, reflecting at the least untidiness and sometimes blatant dishonesty. In July 2006, the United States FDA sent a warning letter to Concord Laboratories of New Jersey, pointing to many faults in the firm's quality control procedures. There had been failure to record the initials or signature of the individual who had carried out each test. On occasion, the chromatographic methods used in testing had been changed, no indication being given in the record as to who had made or authorized the change. The laboratory managers in Research and Development and in Quality Control all had access through a common password to the computer system on which records were kept, so that it was impossible to determine who had made a particular entry or subsequently modified it.

Just occasionally, even in the United States, it is found that persons involved in manufacturing or quality control are not only incompetent or inadequately trained but also admit to the fact. Following inspection in April and May 2007 of Pharmaceutical Laboratories and Consultants in Des Plaines, Illinois, an FDA inspector who had found multiple faults in the firm's quality control procedures also concluded that individuals responsible for supervising the manufacture of drug products lacked the education, training and experience to assure that the products met their specifications. There was in addition no documentation that other employees were trained for the operations they performed in their assigned duties: the president and laboratory manager told the FDA

23 Law of 11 April 1803.
inspector that all training records prior to a certain date had been
discarded, and the firm’s internal training in GMP methods was found to
be far from thorough.25

2.4 THE QUALITY OF ACTIVE SUBSTANCES AND
STARTING MATERIALS

There is as a rule no good reason why a pharmaceutical company should
find itself obliged or even tempted to use starting materials of inferior
quality. Quality standards for many well-known active substances, as
well as details of methods by which they can be made, analysed and their
quality ensured, are to be found in standard reference works such as the
US Pharmacopoeia and European Pharmacopoeia. Complementary vol­
umes (such as the US National Formulary) provide recognized methods
for formulating finished products and ensuring their conformity, and
standards for the most widely employed recipients (i.e. the additives
needed to prepare tablets, solutions, or other forms of administration) are
similarly laid down in the literature. These materials, of recognized
quality, are generally available at competitive prices from well­
established suppliers. Only where a manufacturer proposes either to
introduce an entirely new active substance into medicine or to improve
the form in which a known drug is to be presented will it be necessary to
develop suitable methods in house and to seek approval for these from
the regulatory authority. At that stage these methods are likely to be
confidential matters, protected from imitation by others only by mainten­
ance of industrial secrecy, or they will have been patented. At a much
later phase, once a drug has come into widespread use and perhaps only
as the date of patent expiry approaches, the manufacturer will in all
probability propose to the principal reference works that its standards and
methods be officially recognized and recommended in their volumes.

The situation has become rather more complex in recent years with the
availability of many starting materials at attractive prices from entirely
new and unfamiliar sources, especially in Asia, where products have not
necessarily been manufactured and tested according to global standards.
In such circumstances there is an obvious obligation on the firm
purchasing these materials to check their quality, both when approving an
advance sample and again by testing individual batches as they arrive.

25 IM (2009), ‘Inspector cites Pharmaceutical Labs for laboratory control
and quality system flaws’, Inspection Monitor, June.
In 2007 and early 2008 a large number of serious allergic reactions, including 62 fatalities, occurred among users of the blood thinner heparin, marketed by the US firm Baxter International. The product was temporarily withdrawn from the market. The reactions were traced to the presence in the final product of a chemically altered form of chondroitin sulphate that chemically resembled heparin. The Baxter product had been based on what was supposed to be raw heparin, supplied from Chinese sources and processed by Scientific Protein Laboratories based in China and Wisconsin. When manufacturing the final product at its New Jersey plant, Baxter had not detected the presence of the contaminant and it was not even clear whether it had been present in the material despatched from China or had entered the production process later. By early 2010, many of the injured patients or their estates were bringing civil actions against Baxter International. In the first such case to be decided, in June 2011, a court awarded $625,000 to the estate of a man who had suffered a fatal reaction to the product.

In 2006, Hanford Pharmaceuticals in the US was obliged to withdraw several lots of the antibiotic Cefazolin for Injection after microbial contamination with four organisms had been traced to contamination of the active ingredient used to manufacture the product. The source of the starting material was not stated. The defects identified by the US FDA in Caraco products (see Section 2.1 above and Section 2.9 below) related in part to the ingredients used in manufacturing.

The quality of blood products, which are prepared from blood collected from human donors, is heavily dependent on every donor's state of health, and the manufacturer is clearly responsible for ensuring that each donation is acceptable. During the late 1970s and early 1980s large numbers of haemophiliacs throughout the world became infected with HIV after receiving tainted preparations of clotting factors made by the Armour Pharmaceutical Company, Bayer Corporation (and the latter's

Cutter Biological division), Baxter International (and its Hyland Pharmaceutical division) and Alpha Therapeutic Corporation. It has been estimated that between 6,000 and 10,000 haemophiliacs in the United States alone became infected with HIV.\textsuperscript{32} In 1997, the four firms agreed to pay $660 million to settle cases in the United States. In several countries, including Japan, Iran and Canada,\textsuperscript{33} criminal proceedings were brought against those considered responsible, including in some cases drug company executives, state employees, or agencies providing transfusion services, such as the Red Cross.

Even where a firm manufactures its own active pharmaceutical ingredients (APIs) or excipients, its quality control procedures on these may fall foul of agency requirements, for example if it approves material based on the average results of several tests rather than considering the acceptability of the results obtained in each test. For example, Bayer in Germany synthesized drospirenone, the active ingredient of a number of contraceptive products. The firm received a warning letter from the United States FDA because its internal approval was based on the average result of a number of tests performed on each batch.\textsuperscript{34}

Similarly, if a factory obtains starting materials packed in several containers, material from each individual container will ideally need to be examined since the quality may vary. The acceptable practice may however depend on the source. The SmithKlineBeecham plant in Bristol (Tennessee) used potassium clavulanate from a Glaxo plant in the UK and was in the habit of testing a mixed sample of materials from various containers. The FDA objected that it should have examined material from each container separately. The FDA did not object to the testing of a single sample from one container where amoxicillin material came from one of SKB’s own plants in Singapore that had been FDA inspected, since in that situation it could be assumed that the contents of all the containers in a batch would be identical.\textsuperscript{35} An inspection of Hyaluron’s factory in Burlington, Massachusetts, in 2009 noted a series of defective


\textsuperscript{34} HN (2009), ‘FDA cites Bayer for unapproved quality control measures at German drug factory’, \textit{Health News}, 15 September.

\textsuperscript{35} IM (2009), ‘SmithKline nets a single observation for improper testing of incoming shipments’, \textit{Inspection Monitor}, June.
procedures relating both to the testing of starting materials and the recording of problems experienced during manufacturing.\textsuperscript{36}

Finally, one needs to bear in mind that starting materials, like finished products, may have been tampered with before they arrive; visual inspection is often helpful in excluding such a risk, and the results need to be recorded.

2.5 MANUFACTURING PROTOCOLS AND ROUTINES

As pointed out above, a manufacturer has an obligation, specifically laid down in many regulations, to draw up and maintain a detailed protocol specifying exactly how a pharmaceutical product is going to be produced in agreement with agreed standards and how its quality will be assessed before it is released onto the market. Some variation in the final product may be acceptable, but that will depend on its nature and uses, and the permissible range of variation must be specified in the protocol. Since, for example, the therapeutic dose of a simple antacid in tablet form is unlikely to be exactly defined and a mild degree of over- or underdosage will do no harm, a content variation of 15 per cent or more may be entirely acceptable. At the other extreme, the cardiac glycoside digitalis must be dosed precisely, and only a very slight content variation is permissible if the drug is to be consistently effective and toxic effects are to be avoided. The point is highly relevant in regulatory practice since imposing an unnecessarily stringent requirement can result in a considerable increase in the complexity and the costs of both manufacturing and quality control.

Commonly more than one product will be undergoing production at any given moment and it is essential to keep each operation strictly separated from the others so that cross-contamination is avoided. It is similarly necessary to remove every trace of one product from the equipment before the same production line is used for another. Cross-contamination may be attributable to the layout of manufacturing premises, the practices of individual employees, the procedures for handling and controlling raw materials or the cleaning of equipment and containers, and it may occur at almost any stage of manufacturing.\textsuperscript{37}

\textsuperscript{36} IM (2009), 'Hyaluron slapped with 24-item 483 for inadequate records, testing', \textit{Inspection Monitor}, June.

\textsuperscript{37} Shepherd D (2007), \textit{Cross Contamination in the Production of Pharmaceuticals and Bio-Pharmaceuticals}, Baltimore: PDA Bookstore.
In 2003 in Australia, after 19 people had been hospitalized after using products from Pan Pharmaceuticals, an inspection team found that the firm had been releasing and distributing drugs containing metals as well as quantities of cross-contaminating antibiotics intended for animals. Manufacturing practices were found to be “critically deficient” in nine key areas, including falsification of records, cleanliness and quality control, and the plant was closed down. A thousand workers lost their jobs. This was the largest recall in Australian history, with 1,369 different products recalled and Pan driven into bankruptcy. In 2008, Pan’s founder Jim Selim, who had been on the list of the 200 wealthiest Australians before the disaster, received a $55 million settlement from the Australian government. Selim alleged in a Federal Court case that the regulatory action of the Therapeutic Goods Administration was motivated by ill-will towards him over a 1996 conviction of the company for another allegedly serious GMP violation that had been subsequently reversed on appeal. Selim was also acquitted of criminal charges in the 2003 recall case, but the court imposed a $10 million penalty on various civil charges.

Cross-contamination of products was also among the defects identified by the US FDA at Caraco Pharmaceuticals (see Section 2.1 above). Certain forms of cross-contamination are particularly dangerous. Manufacturing lines for different products must be rigidly separated and the World Health Organization recommends that:

Dedicated and self-contained facilities must be available for the production of particular pharmaceutical products such as highly sensitizing materials (e.g. penicillins), or biological preparations (e.g. live microorganisms). The production of certain other highly active products such as some antibiotics, hormones, cytotoxic substances and certain non-pharmaceutical products should not be conducted in the same facilities ... The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of pharmaceutical products.

Where the principles of Good Manufacturing Practice and even those of a company’s own Standard Operating Procedures (SOPs) have been

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breached, one will need to determine at which level responsibility for the fault lay. Following an outbreak in Britain of cases of injury and death due to bacterial contamination of parenteral fluids produced by Evans Medical, an official report\(^{41}\) identified the fault as the failure of an autoclave to reach sterilizing temperature. As Braithwaite put it in 1984: “When the contaminated batch was produced, the recording thermometer attached to the autoclave failed to indicate a rise in temperature”. This warning was ignored in contravention of SOPs because the recording thermometers had a habit of breaking down. “Hence, an attitude developed where temperature warnings were not viewed seriously.”\(^{42}\)

### 2.6 PACKAGING

Many drugs are packaged using materials and methods that are either well recognized and defined in the literature, or that have been developed and patented by firms specializing in this field. Pharmaceutical companies do however on occasion introduce novel packaging forms of their own devising and here they clearly bear responsibility for ensuring that these provide adequate protection for the product in the circumstances in which it is likely to be used. Some products are particularly sensitive to even minor packaging defects; this applies, for example, to intravenous fluids, generally supplied in plastic bags; puncture of such a bag at any stage will allow leakage of the fluid or permit microorganisms to enter and contaminate it. It is obviously essential that such defects be remedied as soon as they are detected.

One of several elements in a warning letter from the FDA to Pfizer in 2002 concerned multiple complaints from the field, relating to potential non-sterility and leakage of intravenous Diflucan\(^{R}\) (flucanozole) due to a puncture in the bags in which the product was supplied. The FDA noted that the first complaint had been received by the firm on 10 September 2001, and that, despite two more confirmed defects, the product had remained on the market until early February 2002.\(^{43}\)

\(^{41}\) Clothier Report (1972), Report of the Committee Appointed to Inquire into the Circumstances, Including the Production, which Led to the Use of Contaminated Infusion Fluids in the Devonport Section of Plymouth General Hospital, London: Her Majesty’s Stationery Office.


\(^{43}\) Sami T (2003), ‘Pfizer central stability lab nets 5-item 483 for quality, lab controls’, Validation Times, 1 December.
Packaging materials may also be contaminated, for example with microorganisms or particles, and this could have serious consequences where products are intended for injection. At a Novartis plant producing vaccines in Germany, metallic particles had been detected on the tops and undersides of filled rabies vaccine stoppers. According to an FDA inspection report in June 2009, the firm's investigation of this matter had been neither complete nor timely. The problem had first been detected in January 2008, when 100 vials were rejected. No investigation however took place until a further 241 vials were rejected in late February. Although several investigations were then conducted, none was undertaken "to determine the presence of particles in the product or on the undersides of the stoppers" which would naturally be exposed to the content of the vials. When a later in-depth study was carried out, it was found that the metal particles could indeed have contaminated the vaccine.\(^4^4\)

Fluids used for irrigation during surgery can be the subject of similar problems. In February 2006 the FDA noted that 300 complaints had been received after a balanced salt solution had been used for irrigation during cataract surgery or other operations on the eye, nose or throat. Manufactured by Cytosol Laboratories and distributed by various firms under different labels, the solution was found to be contaminated with endotoxins. Among the complaints were reports of a serious and potentially irreversible eye injury (Toxic Anterior Segment Syndrome), occurring when the fluid reached the anterior chamber of the eye.\(^4^5\)

Once a product has left the plant, the manufacturer can hardly ensure that it is responsibly handled, but it should make certain that it leaves the premises in proper order and securely sealed, and that instructions are provided to those handling it as to its sensitivities, mode of storage and shelf life. Occasionally the firm may have reason to believe that a product has been damaged by poor handling in the field, and in that case it will be wise to take steps to withdraw the affected supplies from circulation. In April 2009, GlaxoSmithKline in Britain withdrew a batch of its hepatitis B vaccine having received evidence of its exposure to sub-zero temperatures during transport. The low temperature could have rendered the batch ineffective.\(^4^6\)

\(^4^4\) IM (2009), 'Novartis nets 15-item 483 for problems at German vaccine facility', Inspection Monitor, June.


A manufacturer cannot normally be held responsible for active tampering with its product, such as occurred in 1982 and later, when an unknown person maliciously introduced cyanide into packages of the American product Tylenol® (paracetamol, acetaminophen). In Britain, deliberate contamination of an over-the-counter analgesic Nurofen® (ibuprofen) with a powerful psychotropic agent was reported in 2011, and the perpetrator was successfully prosecuted. It is now increasingly common practice for manufacturers to render certain of their products as far as possible tamper-proof.

Finally, a manufacturer must take prompt action when complaints regarding product quality are received from the field. Even major manufacturers sometimes err in this respect, as in a case involving Pfizer, discussed earlier in this section.

2.7 QUALITY ASSURANCE AND CONTROL

Quality assurance and control are two sides of the same coin. Quality assurance entails a constant effort to ensure the maintenance of standards at every stage of production; quality control is exercised towards the end of the process or, as various phases are completed, in order to ensure that the defined standards have indeed been met and that the outcome has been satisfactory.

The defects identified by the US FDA when inspecting Caraco Pharmaceuticals in 2008 and 2009 (see Section 2.1 above) related in part to faults within the Quality Control Unit. The Unit had among its other shortcomings failed to review and approve all drug production and control records in order to confirm that there had been compliance with established written procedures before a batch was released; nor had it thoroughly investigated any batch or any of its components that had failed to meet the set specifications. A batch of the opiate analgesic tramadol HCl had been found to be contaminated with the beta-blocker metoprolol tartrate, while a batch of metoprolol tartrate proved in turn to

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50 Free Library (2003), ‘Pfizer central stability lab nets 5-item 483 for quality, lab controls’, op. cit.
be cross-contaminated with the antidiabetic drug metformin. The source of the cross-contamination had not been detected, and other batches of the product continued to be released for sale. Release test methods were not validated for the detection of every potential contaminant and had not been shown to be suitable under actual conditions of use. Other faults of Caraco’s Quality Control had included the release of product batches that were still the subject of an investigation into equipment failure, failure to investigate fully cases where content uniformity tests or measurements of dissolution rate had shown unacceptable results, and failure to investigate fully the fact that metformin tablets had proved to contain metal scrapings and foreign matter.51

Stability studies within a factory are sometimes modified to produce more favourable results or are outright falsified. In 2006, inspectors visiting the Paonta Sahib facility of Ranbaxy, one of India’s largest producers, reported that drug samples meant for the necessary testing were stored in refrigerators even though they should have been stored at room temperature in order to provide results applicable to everyday conditions. The logbooks did not specify which samples were in the refrigerator or how long they had been there. A warning letter was duly issued. On a later occasion, however, stability testing again proved to be seriously unsatisfactory, this time with apparent falsification of records. In one instance, results were submitted purporting to show that a drug had been tested at three, six, nine and twelve months when in fact all the stability tests had been conducted on the same day or within days of each other.52,53

Even in countries with high standards and efficient inspection, dishonest practices in quality control are not entirely unknown. Early in 2005 an FDA inspection of Able Laboratories of New Jersey found no serious defects in its manufacturing routines. Subsequently, however, one or more whistleblowers in the company drew the attention of the Agency to possible fraud in the quality control sector. An additional inspection in May 2005 detected serious faults, centring on the fraudulent use of a chromatography data system; results obtained in certain assays were sometimes cut and pasted into other reports. One finding concerned tablets of atenolol, a beta-blocker used in heart and vascular disorders.

The test for dissolution specified that this should under specified conditions attain not less than 85 per cent of the standard content. The test results showed that this was in one instance as little as 30.9 per cent; in the Certificate of Analysis this result had been altered to indicate 102.8 per cent. Similar falsification had occurred with other products, including the central analgesic propoxyphene napsylate. In the light of these and other equally serious findings the FDA withdrew the company's manufacturing licences and cancelled its ongoing new drug applications.\(^{54,55}\) Four members of the staff, including the head of Quality Control, were prosecuted for their role in the fraud.\(^{56}\)

A dubious practice that sometimes comes to light is the replacement of one testing method by another when unfavourable results are unwelcome. When inspectors examined the quality control for rabies vaccine at a Novartis plant in Marburg, Germany, it found that in one test for vaccine processing times the result had been recorded as "failed to pass". A different type of analysis was then applied; a favourable result was obtained and the vaccine was released. The inspection team regarded the overall procedure as unsatisfactory.\(^{57}\)

Quality control must be maintained throughout the period that a product remains on the market, with full control procedures being applied to every batch. If problems arise in maintaining quality standards, the authorities that originally licensed the product should be informed. In November 1995 the Warner-Lambert Company pleaded guilty to a felony charge and was sentenced to pay a $10 million fine for fraudulently failing to notify the federal government about persistent problems encountered in maintaining stable dosages of certain of its drugs, including the anti-epileptic product Dilantin\(^R\) (phenytoin). During several meetings with the Food and Drug Administration, the firm had concealed the problems. A grand jury in Baltimore subsequently indicted Warner-Lambert's former vice-president for quality assurance on charges of

\(^{54}\) FDA (2005), 'Able laboratories products: recall of all manufactured drugs', US Food and Drug Administration Press Release, 27 May.


\(^{57}\) IM (2009), 'Novartis nets 25-item 483 for problems at German vaccine facility', Inspection Monitor, June.
conspiracy, for having shipped adulterated Dilantin and for obstructing FDA proceedings.\textsuperscript{58}

Some such quality defects are detected further down the distribution chain, for example in a retail pharmacy; reports on such findings will normally be sent to the health authorities, who can take up the matter with the manufacturer concerned. Two anonymized examples have been provided by the FDA’s Med Watch Program:

While stocking a box of 15 cc bottles labelled Syrup of Ipecac, a pharmacy technician noticed that one translucent bottle had a much brighter colour than the rest. The FDA was contacted: it found that the bottle contained not Syrup of Ipecac but another agent that, while not toxic, would not produce the desired effect of Syrup of Ipecac if used to treat a case of poisoning. The product was recalled from the market.

A pharmacist observed that a 5cc unit bottle of diphenhydramine syrup made a rattling noise when shaken. After removing the seal, it became obvious that the noise was caused by loose glass fragments floating in the syrup. FDA investigation at the manufacturer’s premises revealed a problem with the production of glass bottles. The product was recalled nationwide.\textsuperscript{59}

Unfortunately, not every defect is so readily recognized before the product reaches the patient. Braithwaite noted in 1984 a hazardous mix-up in Australia in which blister packs supposed to contain the diuretic Lasix\textsuperscript{R} (furosemide) in fact contained the antimalarial quinine hydrochloride.\textsuperscript{60}

If there is any doubt whether a quality defect will harm users, it may be possible to get some indication on this score from field data. At a Novartis plant that was producing vaccines in Germany, there was a temporary failure in the procedure for aseptic filling of the vials and two contaminated vials were found. An inspection team considered that internal follow-up had been inadequate to determine whether subsequent production had been sterile or not. The firm’s own pharmacovigilance unit had in fact requested a medical review of adverse reaction reports from the field. Three reports of suspected adverse events were found –


\textsuperscript{60} Braithwaite, \textit{Corporate Crime in the Pharmaceutical Industry}, op. cit., p. 113.
one involving an injection site abscess and two concerning inflammation at the injection site.\textsuperscript{61}

One fundamental principle in quality control is that the selection and testing of samples must be carried out by a separate unit, employing staff who are not themselves involved in production; production staff may be all too inclined to approve batches with which they have been involved or they may simply lack the correct routine. An element which may well have been relevant in the release of contaminated parenteral fluids produced by Evans Medical in Britain (see Section 2.5 above) was the fact that, in the absence of firm rules on sampling from Quality Control, the production staff themselves selected samples for analysis. In doing so they took samples only from the top layer of each cage, apparently because this was the easiest course. In fact the contamination seems to have been present only in the lowest layer of the cage and therefore went undetected.\textsuperscript{62}

Both with respect to quality assurance and other aspects of manufacturing, a regulatory agency or inspectorate may find that a firm fails to deal adequately with defects that have been detected. In March 2013, the United States FDA noted that Alexion Pharmaceuticals of Cheshire CT had failed to correct fully a series of defects observed during inspection the previous year. These related inter alia to bacterial contamination of Soliris API (eculizumab), failure to verify the effectiveness of a room cleaning procedure, and use of a toxicological assessment routine which failed to take into account the fact that the product concerned was intended for paediatric use. The firm was warned that continuing failure to correct procedural faults could result in legal action, seizure or injunction.\textsuperscript{63}

A typical example of such a seizure was reported by the FDA in 2005 when the Agency, together with the Department of Justice, seized stocks of Paxil CR\textsuperscript{R} (paroxetine and Avandamet\textsuperscript{R} (rosiglitazone) tablets manufactured by GlaxoSmithKline which failed to meet the standards laid down by the FDA to ensure safety, strength, quality and purity. Although the FDA was not aware of any harm done to consumers by the products in question, the defects detected could have resulted in patients receiving

\textsuperscript{61} IM, ‘Hyaluron slapped with 24-item 483 for inadequate records, testing’, op. cit.
\textsuperscript{62} Clothier Report, Report of the Committee Appointed to Inquire into the Circumstances, op. cit.; see also Braithwaite, Corporate Crime in the Pharmaceutical Industry, op. cit., at pp. 118–19.
an incorrect dosage or release form. Glaxo had already voluntarily recalled some of the affected lots, but its failure to recall the remainder was the immediate reason for the seizure.64

It is impossible to determine whether the incidence of serious product defects and mix-ups has risen or fallen in recent years; the consumption of pharmaceuticals has grown, as has the stringency of inspection, and both factors would lead to a rise in the number of reported cases even if there had been a general improvement in compliance. In some fields it would seem that there have been significant advances. Two massive outbreaks of fatal septicaemia in the United States in the 1960s and early 1970s were traced to microbial contamination of parenteral fluids supplied by the Abbott company which had breached GMP requirements.65 Thirty years later, when the Centers for Disease Control (CDC) reprinted their original account of these events, they were able to add that, as a direct consequence of these cases, FDA and CDC standards had improved, as had surveillance for outbreaks potentially attributable to contaminated products; no further nationwide outbreak of bloodstream infections attributable to contaminated intravenous solutions had occurred.66

2.8 RECORD KEEPING

At every stage of production and quality control, detailed records must be kept, both to maintain standards and to provide reliable data for management and for external inspection, especially when a fault is suspected.67 If any procedure is changed, the change must be recorded.68 Who had responsibility for the procedure? Why was the change made? Who made it and who authorized it? Have the possible consequences of the change been evaluated? Is the change in procedures in line with protocols earlier

68 IM, ‘Novartis nets 15-item 483 for problems at German vaccine facility’, op. cit.
approved by the authorities? Both health and lives may depend upon finding correct answers.

The importance of trustworthy records in tracing the staff members responsible for particular acts or omissions is evident. A record must also be made in such a manner that it cannot subsequently be altered, even with the best of intentions. Needless to say, the intentions are not always of the best. There may, as noted elsewhere in this chapter, be a desire to hide mistakes, to glorify figures or quite simply to cut corners.

2.9 PROTECTION OF EMPLOYEES

The western pharmaceutical industry itself has often stressed the extent to which its employees enjoy protection from risk as a result of extensive safety precautions. Various authorities independent of industry have also confirmed that in sophisticated markets "... working conditions in pharmaceutical plants are better than those in most other manufacturing plants, and work-related injuries are rare".69 It is much less certain what proportion of firms maintain such safety standards in the developing world or in countries that have only during the last generation entered the field of pharmaceutical manufacturing.

General industrial safety legislation can go a long way towards ensuring that workers are not injured, but there is a need for supplementary rules to cover the special situation of pharmaceutical manufacturing. Particularly strict precautions must be taken to protect the relatively small number of employees who work with infectious cultures and poisonous chemicals.70 It may, all the same, be impossible to avoid completely some degree of risk where highly potent active substances are being manufactured or processed. The individual needs to be protected from purely accidental exposure but also from his or her own carelessness, and safety training at all levels is essential.

In fact, only a minority of the work-related injuries in the pharmaceutical industry reported to Britain's Health and Safety Executive over the period 2001–04 related specifically to exposure to active substances. There were some 430 instances of manual handling injuries or upper

70 Ibid.
limb disorders such as might have occurred in any form of manufacturing; by contrast there were only 150 cases of occupational dermatitis and 23 instances of occupational asthma.\textsuperscript{71}

Such problems as may result from exposure have been reviewed at various times, for instance by Watrous as early as 1947\textsuperscript{72} and by Heron and Pickering in 2003.\textsuperscript{73} Particular concerns have arisen with the oestrogens, some of which are active in microgram doses. As early as 1942, Scarff and Smith noted the development of gynaecomastia (breast enlargement) and loss of libido in men working with the non-steroidal oestrogen diethylstilboestrol.\textsuperscript{74}

A generation later, Harrington et al. looked at workers exposed to steroidal oestrogens. Of 25 men studied, five were found to have effects linked to steroid influence, including gynaecomastia, loss of libido and galactorrhoea. Of 30 women, 12 were found to have menstrual breakthrough bleeding, a rate four times higher than that recorded in a control population.\textsuperscript{75} In the early 1980s, a Wyeth plant in Windsor, Ontario was the subject of particular scrutiny since workers in the plant were themselves concerned about exposure to ethinylestradiol, used in the oral contraceptive Ovral\textsuperscript{R}. Marshall found evidence that male and female employees were exposed to the components in sufficient quantities to lead to symptoms and serious adverse health effects.\textsuperscript{76} Government inspectors found a number of points of exposure that needed to be dealt with and they imposed requirements that in part met the workers' demands.\textsuperscript{77}

\textsuperscript{71} HSE (2005), Injury Statistics in the Pharmaceutical Industry, London: Health and Safety Executive.
\textsuperscript{72} Watrous RM (1947), 'Health hazards of the pharmaceutical industry', \textit{Brit. J. Industr. Med.}, 4, 111–25.
\textsuperscript{73} Heron RJL and FC Pickering (2003), 'Health effects of exposure to active pharmaceutical ingredients (APIs)', \textit{Occupational Medicine}, 53, 357–62.
\textsuperscript{74} Scarff RW and CP Smith (1942), 'Proliferative and other lesions of the male breast in stilboestrol workers', \textit{Br. J. Surg.}, 29, 748–9.
\textsuperscript{75} Harrington JM, GF Stein, RO Rivera and AV de Morales (1978), 'The occupational hazards of formulating oral contraceptives – a survey of plant employees', \textit{Arch. Environ. Health}, 33, 12–15.
\textsuperscript{76} Cited in Nelson M and R Moure (1980), Health hazard evaluation. Wyeth Pharmaceuticals. Local 9-368, Windsor: Oil, Chemical and Atomic Workers Union.
\textsuperscript{77} Wigmore D (2009), \textit{Pharmaceuticals Manufacturing: What do we know about the occupational health and safety hazards for women working in the industry?}, Canada: Women and Health Protection.
In a similar but more recent study, Shamy et al. examined 18 males and 34 female workers exposed to ethinyloestradiol, levonorgestrol and progesterone in the manufacture of oral contraceptives in Egypt. The women selected for study were principally performing blister packaging tasks and had been post-menopausal for at least two years. Oestrogen levels were found to be significantly increased in both sexes and there was a decrease in testosterone levels in the male workers.\(^7\)\(^8\)

In other instances, too, drugs to which workers are exposed may induce precisely the pharmacological effects that one would expect, or may cause allergic reactions. A report from Italy in 1993 described a case in which an operator working for five days on the manufacture of the antidiabetic drug glibenclamide was admitted to hospital in hypoglycaemic coma; it appeared that he had inhaled the drug that was present in the form of microparticles in the factory air.\(^7\)\(^9\)

In December 2010, Britain’s Health and Safety Executive successfully prosecuted Catalent Pharma Solutions of Swindon after 18 employees of the firm developed irreversible allergic contact dermatitis as a result of exposure to the antipsychotic drug olanzapine. The risk was known but the firm had not taken timely measures to prevent exposure to the substance even after cases had been reported. Catalent was fined £50,000 and paid a similar sum in costs.\(^8\)\(^0\)

In certain instances only biological testing will be able to detect the consequences of exposure and if there is any risk of such exposure routine testing may be called for. A British report in 1986 described how operators of semiautomatic encapsulating machines were found to have absorbed biologically detectable amounts of the barbiturate quinalbarbitone, apparently through the skin. Staff wore overalls and caps but no gloves or masks. Quinalbarbitone had been fed into the machine by hand.\(^8\)\(^1\)

Since some pharmaceuticals have carcinogenic potential, a number of studies have looked for cancer outcomes in pharmaceutical workers exposed to various agents in the course of their work. In a US plant


study, excess rates of respiratory cancer were found in male maintenance workers and female production workers. There was also an increased relative frequency of melanoma among males and of leukaemia among females in production.\textsuperscript{82}

A slightly raised incidence of cancer deaths was found among British male pharmaceutical workers, particularly relating to the urinary tract and pancreas.\textsuperscript{83}

Dutch researchers found evidence of a common cytostatic drug in the inhaled air and in the urine of four laboratory and manufacturing workers, due to contamination in the workplace.\textsuperscript{84}

The extent of the precautions needed to ensure workers' safety when dealing with substances as toxic as these cytostatic agents has been illustrated in a series of papers by a university group at Lyons, France, who examined various cytostatic agents produced in capsule form. Whereas one might expect the outer surface of filled and sealed capsules to be clean, this surface proved in fact to be contaminated with the drug substance; this was demonstrated for six different anti-cancer agents supplied by various manufacturers, which meant in practice that the filled capsules should only be handled by persons wearing protective gloves.\textsuperscript{85}

At one manufacturing site, atmospheric levels of the cytostatic methotrexate as high as 182 \( \mu g/m^3 \) were found in the area in which the powders were dispensed. Significant levels of methotrexate were found in the urine: since the workers in the area wore a high level of respiratory protection, the investigators concluded that skin absorption was a major factor.\textsuperscript{86} Findings with 5-fluorouracil were very similar.\textsuperscript{87}

\textsuperscript{82} Thomas TL and P Decoufle (1979), 'Mortality among workers employed in the pharmaceutical industry', \textit{J. Occup. Med.}, 21, 619–23.
\textsuperscript{84} Bos RP, BFJ Weissenberger and RBM Anzion (1998), '\( \alpha \)-fluoro-\( \beta \)-alanine in urine of workers occupationally exposed to 4-fluorouracil in a 5-fluorouracil-producing factory', \textit{Biomarkers}, 3, 81–7.
Respiratory sensitization has been noted in relation to exposure to several compounds during the manufacturing process, notably the penicillin and cephalosporin antibiotics and various enzymes.

There has been a series of expressions of concern regarding possible risks faced by women working in pharmaceutical factories;88 the issue is also raised in certain of the papers already cited. In Denmark in 1994, an increased risk of breast cancer was reported among female production workers handling insulin (and perhaps among long-term male workers as well), although the causal links were not entirely clear.89

Pregnant women in pharmaceutical factories may constitute a special risk group, since exposure to some substances—notably organic solvents—has been thought to raise the risk of abortion.90 One might also anticipate risks with exposure to oestrogens during pregnancy. A Finnish group conducted a register-based, case-control study on the pregnancy outcome of female workers in eight pharmaceutical factories in Finland to determine whether they had a higher risk of spontaneous abortion than the general population or matched controls. In a logistic regression model the odds ratio was increased for women exposed to oestrogens.91

Explosions are today rare in European and American pharmaceutical factories, and accidents with machinery92 no more common (and no less avoidable) than in other areas of manufacturing. Acute accidents in manufacturing plants may occur without criminal responsibility devolving on any particular person or fault, but on occasion things go wrong as a result of negligence or poor management. In 1984 John Braithwaite considered the case of a major explosion at a plant owned by the Warner-Lambert pharmaceutical company on New York’s Long Island, though that particular plant was in fact producing nothing more dangerous than chewing gum and the explosion was due to contamination of the air with magnesium stearate particles. The company’s insurers had warned the firm that there was a severe explosion hazard at the plant, but the warning

88 Wigmore, Pharmaceuticals Manufacturing, op. cit.
was virtually ignored. In due course there was indeed an explosion, accompanied by an outbreak of fire. Six workers were killed and 55 others seriously injured. In 1980 the victims or their estates brought a civil action against the company, but since the immediate cause of the ignition could not be determined with any certainty the claims were dismissed.93

It is not clear how a similar case would be dealt with at the present time, but occupational health law has progressed a long way since 1980, though sometimes hesitantly, and one senses that under current law in most western countries the company's failure to take account of a warning from its insurer would play a significant role in judging subsequent claims resulting from injury or death. Nor would one have expected the inability of the plaintiffs to define the factor immediately triggering the explosion to undermine their case; the presence in the air of a potentially explosive dust, to which management had been alerted, was the basic fault that should have been identified and corrected before any explosion could occur.

Elsewhere, explosive accidents have similarly been uncommon, but one must note a case from Japan that was the subject of a somewhat unusual assessment. In 1998 an explosion occurred at a Japanese pharmaceutical factory, injuring five employees. The immediate cause was the explosion of ethanol vapour due to insufficient ventilation during the drying of vitamin tablets. An investigation of the precipitating causes of the accident concluded however that there could have been numerous failures in management and supervision. The list proved to be almost encyclopaedic: the investigators spoke of “Poor Value Perception, Poor Safety Awareness, Inadequate Risk Recognition, Organizational Problems, Poor Management, Poor Operation Management, Carelessness, Insufficient Precaution, Carelessness of Operator, Planning and Design, Poor Planning, Poor Operation Planning, Malicious Act, Rule Violation ... Safety Rule Violation”.94

Whether these multiple factors were indeed likely causes of the accident, or were simply intended as hypotheses for the litigation lawyers


to advance, history does not relate; one could however hardly wish for a better listing of the faults to be avoided if pharmaceutical manufacturing is to be rendered acceptably safe.

If risks to safety, health and the environment are to be all but eliminated, effective process design will be vital. As Bennett and Cole have pointed out, it is a trend that must continue if work in this industry is to be considered safe: effective process design was built up in the nuclear, fine chemical and petrochemical industries; the pharmaceutical industry was initially slow to apply this knowledge but it is now being used in both primary and secondary production. 95

In view of all the uncertainties attached to exposure to pharmaceutical materials, the only defensible approach to the problem for management is simply to reduce exposure to the lowest level attainable or to identify a means of eliminating it completely. In case of doubt, regular clinical testing of exposed subjects to detect circulating levels of active substances is surely advisable.

2.10 ENVIRONMENTAL RISK

Pharmaceutical production inevitably results in the creation of a great deal of solid and liquid waste material, ranging from superfluous amounts of synthetic substances to animal material from which useful substances have been extracted, and some of this is likely to enter the environment. The United States Environmental Protection Agency lists a large number of pharmaceutical products and intermediaries that must be considered as toxic waste and must be destroyed or disposed of in an appropriate manner if they are not to contaminate the environment. 96 A particular difficulty is to determine to what extent the contamination of the environment by pharmaceuticals and related substances is due to their excretion by patients who have used them rather than to contamination at the factory level. It is almost certain that the bulk of such contamination is due to the fact that the human and animal body excretes in the urine and faeces either active drugs or metabolites, the latter resulting for example from changes that have taken place in the liver.

Whatever the source, concern here as in other matters reflects in particular the very high potency that many of these compounds possess; in particular it has been found that synthetic hormones remain fully active for long periods when they enter the environment. Presence of antibiotics in low concentrations can lead to the emergence of resistant strains. Animal populations can be significantly affected; there is evidence of sexual changes in fish in inland waters in various countries. 97, 98

*Water pollution* has for some decades been a matter of concern. 99 Insofar as waste disposal and effluents are involved, there is a need to adhere very strictly to the requirements of environmental law if unwanted effects resulting from pollution of the atmosphere or of water supplies are to be avoided. In December 2012 Ireland’s Environmental Protection Agency successfully prosecuted Baxter Healthcare on charges relating to the unlicensed discharge of waste into sewers, failure to store waste in segregated areas and changes in production routines that could result in breach of environmental obligations. 100

Pollution of natural water resources and/or of piped water supplies is a commonly cited offence in cases brought against pharmaceutical companies. In 1992 Bristol-Myers Squibb pleaded guilty to charges of illegally discharging chemical pollutants into the Onondaga Country Metropolitan Treatment Plant at Syracuse, New York, in late 1987 in violation of the federal Clean Water Act. The company paid $3.5 million in criminal fines and penalties and agreed to build a pre-treatment facility that would cost at least $10 million. 101

In 1997 Warner-Lambert Inc. pleaded guilty to falsifying reports on the levels of pollutants that it was releasing from its wastewater treatment plant at Vega Baja, Puerto Rico, into a drainage channel that fed the Cibuco River. It agreed to pay a $3 million criminal fine. The company also agreed to pay a $670,000 civil penalty for routinely releasing

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97 Berwyn B (2010), ‘Pollution causes gender-bending in Canadian fish’, *Summit County Citizens Voice*, 1 August.
99 As early as the 1960s, oestrogens in the River Thames reached detectable levels, apparently as a result of the widespread use of oestrogen-based drugs (especially as oral contraceptives became popular) in and around London.
101 Corporate Crime Reporter (1992), 18(3).
excessive levels of pollutants between 1992 and 1995, violating its wastewater discharge permit on 347 occasions.\textsuperscript{102}

In 2008 the US Environmental Protection Agency fined BioMarin Pharmaceutical $119,717 after its Novato, California, facility violated the Clean Water Act numerous times by discharging acidic wastewater into the Novato Sanitation District domestic sewer system and the Ignacio Wastewater Treatment Plant, both of which discharge onto intertidal flats at San Pablo Bay.\textsuperscript{103}

In the summer of 2006 there was extensive death in the fish population of Wissahickon Creek, Pennsylvania; the creek also became unusable as a source of drinking water. The problem was traced to a one-day discharge of potassium thiocyanate into the creek from a plant owned by Merck. The company settled charges brought under the Clean Water Act, paying penalties in excess of $1.5 million and undertaking to invest some $9 million in environmental projects and $10 million in installations to prevent a recurrence.\textsuperscript{104}

Although in a number of studies conducted in western countries the concentrations of pharmaceuticals in drinking water, when related to average water intake, were generally more than 1,000-fold below the lowest clinically active dosage,\textsuperscript{105} the problem is becoming increasingly severe. Here, as in other respects, the steroidal oestrogens have received particular attention because of their potency. At an early stage in the manufacture of oral contraceptives from 1960 onwards, western companies found it necessary to take particular precautions to avoid unwanted effects on nearby populations, but in other parts of the world problems have continued to emerge. Cui et al. found significant levels of

\textsuperscript{102} Corporate Crime Reporter (1997), 37(3).
several oestrogens in the wastewater treatment plant of a factory producing oral contraceptives in China. The proportion removed during treatment varied from 67 per cent to 85 per cent, which meant that a considerable quantity could remain in the water when it was released.\textsuperscript{106}

Air pollution is today of similar concern: ventilation systems installed to protect workers inside a factory may pollute the outside environment instead. In 2001, the United States Environmental Protection Agency charged a Puerto Rico plant owned by Schering-Plough with violating regulations under the Resource Conservation and Recovery Act and aimed at preventing emissions of toxic chemicals into the air. The agency sought in this case a penalty of $82,500 and ordered immediate compliance with the rules.\textsuperscript{107}

Ireland’s Environmental Protection Agency brought a prosecution against Schwarz Pharma in 2006. The firm pleaded guilty to 11 charges of atmospheric pollution: emissions had been 35 times the level authorized in the firm’s licence.\textsuperscript{108} In 2008 Pfizer agreed to pay a $975,000 civil penalty to resolve alleged violations of the Clean Air Act at its former manufacturing plant in Groton, Connecticut, resulting from a failure of its leak detection and repair programme. The company had made use of a range of substances classified as hazardous air pollutants under the Act. Specific violations were stated to include failure to properly conduct pressure tests to identify leaks, repair leaks before start-up, equip open-ended lines with a cap or other seal, and document leak tests to establish full compliance.\textsuperscript{109}

In September 2012 it was reported that the Harbin Pharmaceutical Company in China’s Heilongjiang province had found itself obliged to relocate after major atmospheric pollution had occurred around its plant.


The firm had been fined 1.23 million yuan for failing to meet environmental requirements as well as for improperly storing and burning toxic waste.\textsuperscript{110} It was reported at the time that in parts of China the problem of pharmaceutical pollution was "out of control".\textsuperscript{111}

The US Environmental Protection Agency has on various occasions issued regulations to deal specifically with the issue of hazardous air pollutants from pharmaceutical manufacturing operations, and there appears to have been a progressive increase both in the detail specified in the requirements and in the level of the penalties available in the event of contravention. The rules have sought to reduce emissions of toxic air pollutants (including methylene chloride, methanol, toluene and hydrochloric acid) from the manufacture of pharmaceutical products. It has been estimated that effective control would reduce air toxins annually by approximately 24,000 tons or 65 per cent from contemporaneous levels. The pharmaceutical manufacturing processes affected by the rules include both chemical synthesis and final formulation. The standards set by the Agency appear to be readily attainable and affordable, and there would therefore seem to be no valid reason for breaching them. The solution lies in both purification of ventilation air before it is released but also in a modest modification of working procedures so that toxins are not released into the atmosphere at all. Available techniques include the use of regenerative thermal oxidizers and caustic scrubber systems, which are claimed to remove more than 99 per cent of contaminants.\textsuperscript{112}

It is fair to add that many pharmaceutical companies are attempting to identify and apply means of lessening the environmental impact of their own drug production,\textsuperscript{113} but in Europe the industry as a whole is still among the parties strongly opposing firm corrective legislation.\textsuperscript{114}

\textsuperscript{110} Xinhua News Service (2012), 'Chinese pharmaceutical plant to relocate after pollution scandal', 5 September.
\textsuperscript{111} Hepeng J (2011), 'Pharma pollution is out of control in China', \textit{RSC Chemistry World}, June.
\textsuperscript{114} Gilbert N (2012), 'Drug-pollution law all washed up: EU initiative to clean up waterways faces tough opposition', \textit{Nature}, 27 November.
2.11 PRODUCTION IN DEVELOPING COUNTRIES

Particularly in developing countries, a fair proportion of the medicines on sale, even for serious and potentially fatal conditions such as malaria, are found to be of substandard quality. This reflects, at least in part, the extent to which these countries are dependent for their drug supplies on fraudulent manipulators outside the mainstream (see Chapter 5). In the QAMSA study of the quality of antimalarials circulating in Sub-Saharan Africa, published in 2011, 267 samples were fully tested in the laboratory. Of these, 28.5 per cent failed to comply with specifications, while extreme deviations likely to have adverse consequences for health were found in 11.6 per cent.\footnote{WHO and US Pharmacopeia (2011), Report on QAMSA Study (‘Quality of Anti-Malarials in Sub-Saharan Africa’), Geneva: World Health Organization.}

Some of the drugs in question emanate from known firms based in the industrialized world, but others are produced by fraudulent producers and counterfeiters, largely in the developing world; these are considered in Chapter 5. Issues such as quality control may be particularly tricky where cultural traditions, for example regarding staff procedures or hygiene, are involved. In a dispute, dealt with by arbitration between an American licensor and an Indonesian licensee, the latter was accused of lack of adequate hygiene in manufacturing. One specific complaint was that workers and visitors in the “clean” unit did not put laundered covers over their shoes when entering the section. The Indonesian view was that since it was customary in that country for all to enter such a unit on bare feet, washing them thoroughly beforehand, neither shoes nor covers were relevant. The arbiter in Singapore had some sympathy with this view.\footnote{Dukes MNG (2009), ‘Consultancy notes’, Jakarta (unpublished).}

None of this should obscure the fact that some production of medicines in the developing world attains a commendable standard, often despite difficult conditions, limited finance, a shortage of skilled labour and inconsistent or incomplete control by the health authorities.

2.12 OFFSHORE ABUSES

In common with other manufacturing sectors, though to a greater degree than most, the pharmaceutical industry does make extensive use of offshore bases to avoid taxation (see Chapter 6). Offshore operations may also be used to evade effective controls on manufacturing and quality assurance. In March 2013 a supposedly British firm (Rotapharm) was
suspected of supplying Kyrgyzstan with inferior medicines which were ineffective and possibly harmful; a government commission was investigating the case. In fact it appeared that the firm was based in the British Virgin Islands (with only a nominal office in the United Kingdom), was owned by a Belorussian citizen, and supplied medicines made in Egypt.\textsuperscript{117} When drugs are produced that fail to meet standards in a sophisticated national market, dumping of those batches in a country with less exacting quality standards continues to be a problem.

2.13 THE CHALLENGE OF NANOTECHNOLOGY

The pharmaceutical industry is accustomed to working with materials measured in milligrams and micrograms, but science is currently advancing to a point where materials and structures measured in mere nanograms (i.e. at the molecular scale) will play a role in medicine. America's National Institutes of Health define nanotechnology as "the understanding and control of matter at dimensions of roughly 1 to 100 nanometers, a scale in which unique properties of materials emerge that can be used to develop novel technologies and products".\textsuperscript{118} The introduction into the body of nanotherapeutic and nanodiagnostic agents will probably render it possible to solve longstanding problems in medicine. Among the possibilities already under discussion are the transport of drugs across the blood-brain barrier to treat cerebral tumours, the detection and destruction of micrometastases and the introduction of corrective genes into human cells. Although the initial challenges will be those facing research, issues of manufacturing and quality control will follow. Significant risks are likely to be associated with accidental exposure to active nanoparticles during research or manufacture, and broader issues will arise of dangers associated with the escape of nanomaterials into the environment. The field is at the present time insufficiently developed to assess the prospects and risks. It is however clear that the pharmaceutical industry is likely to find itself heavily committed to work in this area and that the many standards and guidelines existing in the pharmaceutical

\textsuperscript{117} Leigh D and Hall J (2013), 'British firm accused of supplying poor-quality drugs to Kyrgyzstan', \textit{Guardian}, 4 March.

\textsuperscript{118} National Institutes of Health (2008), 'Nanotechnology at the National Institutes of Health; Innovative medical research at the molecular scale', NIH Publication No. 08-6443, pp. 1–8.
area are likely to require massive change and supplementation if they are to provide relevant guidance in nanotechnology.¹¹⁹

2.14 CONCLUSION: WEIGHING UP THE EVIDENCE

In the world of pharmaceutical manufacturing almost every rule in the book has at some time been breached without good reason, sometimes on numerous occasions and by many companies. This may reflect faults at any level, occurring despite the fact that this is a field in which standards and procedures have been clearly laid down and are widely agreed to be necessary.

Do companies care? Too often it would seem that, in the area of manufacturing, a corporation may be primarily concerned with building an image of honesty and quality in order to mask the fact that it proposes to continue behaving in a manner convenient to itself. One could cite examples from many firms, but a single case may suffice:

In October 2010 it was reported that GlaxoSmithKline had agreed to pay $750 million to settle criminal and civil charges that the company had for years knowingly sold contaminated baby ointment and an ineffective antidepressant. Altogether the firm sold 20 problematical drugs manufactured at a very large plant in Puerto Rico that for years was rife with contamination. Cheryl Eckard, the company’s quality control manager, warned of these problems, but instead of solving them the company was reported to have dismissed her.¹²⁰

Faults as regards manufacturing are not the most widely discussed of the industry’s failings. Indeed, when Corporate Crime Reporter editor Russell Mokhiber set out to identify the 100 top corporate criminals of the 1990s¹²¹ and 2000s,¹²² offences connected with drug manufacturing occupied only a modest place on the list. This when 12 of his 20 top


corporate criminals of the 2000s were pharmaceutical companies overall, up from 6 of the top 20 in the 1990s. In both decades a pharmaceutical company topped the Mokhiber list, Hoffman-La Roche in the 1990s, Pfizer in the 2000s. On these lists and in the public and political debate much more attention is usually devoted to evidence of overpricing, antitrust offences or untruthful promotion. Unhappily, the old saying that a doctor's errors lie quietly in the churchyard has some relevance here. Contaminated injections, toxic eyewashes, syrups full of glass splinters – all these things injure, maim and kill. While overpricing and untruthful advertising may be traced back to faults at the management level, failings in manufacturing, such as those that are cited by Mokhiber, appear in many cases to result from offences much further down the corporate hierarchy. That is however no excuse – it is management's job to ensure conformity with good and legal practice at every level.

What is particularly unforgivable is the manner in which a number of companies, having been officially alerted to deficiencies in their manufacturing or quality control procedures, procrastinate in the necessary follow-up. It is true that inspectorates commonly cannot prove that these defects are having adverse consequences for health, but this is no reason to tolerate a failure to meet agreed standards and to correct errors promptly. While certain developments – such as the evolution of the Pharmaceutical Inspection Convention – offer signs of hope, the situation as a whole is still far from satisfactory. Manufacturing standards in some other parts of the world, and particularly in some developing countries and newly industrializing countries, still vary greatly, and their variation can have serious consequences. Our conclusion, then, is that this is one area in which, while there has been genuine progress by "big pharma" in manufacturing in developed economies, this must be set against some serious concerns, such as the fact that pharmaceutical companies as a group continue to behave like firms selling more mundane products, such as clothing and computers, in that they increasingly decide to buy from foreign factories things that they used to make themselves. Quality control on blue jeans or even computers is however rather simpler to manage than quality assurance on pharmaceutical ingredients. The shift from making to buying is the reason why recent progress towards strengthening international cooperation on inspection is so important. We have concluded that when unsafe or environmentally destructive manufacturing does occur, it is usually difficult for regulators in the country where the manufacturing takes place to conclude who, if anyone, has been responsible. It is doubly difficult to do so when ingredients have been manufactured in other countries. The transnational nature of the challenge in regulating medicines is a general one that we attempt to
address in a strategic way in Part III. The challenge of getting better, more just, insider information on who did what on the factory floor and in the management hierarchy is our priority in the analysis presented in Chapter 10.
3. Aggressive or misleading promotion

Whatever the Diagnosis … LIBRIUM

(Headline of Hoffman La Roche advertisement for a tranquillizer, c.1969)

3.1 WORDS, IMAGES AND MEDICINES: WHY CARE?

3.1.1 The Notion of Truth

It is simple enough to declare that the acceptability of drug advertising and promotion must be assessed in the light of the true facts. However, the quest for a definition of what constitutes truth is at least as frustrating where most medicines are concerned as in any other field. As noted in Chapter 1, even the picture of a drug’s safety and efficacy that is drawn by a committee of experts at the moment that it is licensed is only a provisional sketch that will necessarily be supplemented by experience in the field as time – sometimes a long time – goes by. Acetylsalicylic acid (Aspirin) was used without reservation to treat feverish infants from the time of the drug’s introduction in 1899 until, many decades later, a causal link between such treatment and the serious complication known as Reye’s syndrome was suspected and later confirmed (Section 1.7). More than 40 years on, even that intensively studied link remains an indistinct and irregular one, perhaps involving some genetic predisposition; the debate on selecting the safest treatment for children with fever therefore continues. The fact is that the evidence in these matters is continuously evolving and often the subject of controversy.

Even where a degree of certainty has been attained, it is likely to involve qualified conclusions. In 2003 the statement by a vice-president

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of GlaxoSmithKline at a scientific meeting that most prescription drugs are effective only in a proportion of the patients who take them\(^4\) hit the headlines and actually appears to have inspired a popular lyric,\(^5\) but it was no more than a frank, if simplified, statement of the facts. The speaker went on to make the point that drugs for Alzheimer’s disease worked in fewer than one in three patients, whereas those for cancer were only effective in a quarter of patients. Drugs for migraine, for osteoporosis, and for arthritis worked in about half the patients. Most drugs were effective in fewer than one in two patients, mainly because the recipients carried genes that interfered in some way with the effects of the medicine. It is also known that various types of medicines become progressively less effective in the individual patient when they are taken over a longer period.

Against this background, one must also recognize that the process of selling commercial products in a competitive market has always involved a degree of hyperbole and no doubt always will. The audience for advertising has some appreciation of that, and may even enjoy weighing the various alternatives with which it is confronted, taking certain exuberant elements with a grain of salt. That audience must not however be misled by outright falsehoods or misleading suggestion. Truth, insofar as it has been established, is not a commodity that the law allows to be adjusted to suit commercial convenience. In 1991 a British gastroenterologist submitted a complaint under the Code of Practice of the British industry association (ABPI) regarding a report, distributed by Astra Pharmaceuticals and based on a congress paper, regarding the safety profile of the anti-ulcer drug omeprazole (Losec\(^5\)); the company’s summary of the evidence was presented under the heading “Safety confirmed”. The complaint was upheld by the ABPI committee concerned on the grounds that “it was impossible to substantiate a claim that safety had been confirmed for any product”.\(^6\)

Finally, in assessing the acceptability of advertising one must consider not only its content but also its volume. If the physician or the lay consumer could compare commercial messages on equal terms with objective sources of information one might have a basis for sound judgement; in practice, however, the commercial presentation grossly

outweighs and overwhelms the quiet flow of data from impartial sources; the commercial view is presented loudly, aggressively and repeatedly.

A retrospective academic study of pharmaceutical advertising in the United States during 2004 estimated that the US pharmaceutical industry was spending almost twice as much on promotion as on research and development. The authors concluded that the total amount spent on pharmaceutical promotion in 2004 amounted to $57.5 billion, to which must be added a further sum for promotional activities not covered by the study such as off-label sales activities, ghostwriting and seeding trials. In all some 371,000 meetings for promotional purposes were held during the year and the industry was estimated to have spent approximately $61,000 on promotion per physician during that period. The findings on the volume of promotion as compared with expenditure on research are broadly in line with those reported earlier by the US Securities and Exchange Commission.

No one can be in doubt today that advertising and promotion have played a major role in making the pharmaceutical industry one of the most lucrative sectors of business. To paraphrase a well-known saying: some drugs are born great, some achieve greatness and some have greatness thrust upon them - by promotion. The latter are those "me-too" compounds, which would remain part of the grey undistinguished mass were it not for the fact that advertising endows them with an aura that propels them to the top of the market. In an ideal world the market would be dominated purely by those medicines that are best in scientific terms and most responsive to major public health needs, rather than by those that are loudly trumpeted. The only respectable form of publicity is in this view that which, however emphatically, simply emphasizes the truth and enables the most meritorious products to reach the peak of the market rather more quickly than they would otherwise do.

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8 USSEC, as quoted by Laing RD (2001), 'Health and pharmacy systems in developing countries', paper delivered to the WHO/WTO Workshop on Differential Pricing and Financing of Essential Drugs, Høsbjør, Norway, 8-11 April.


10 A "me-too" drug, in industry parlance, is one that is no better than those already on sale and that adds nothing to the range of treatment already available, but that is introduced simply in order to gain market share.
So why care? From the public health point of view, some of the important reasons to be concerned about promotion practices in the drug field are inherent in the above. In a period of economic uncertainty, such as has characterized the opening years of the twenty-first century, the high costs of providing health care have become a subject of widespread debate, and the costs of such care are substantially influenced by the costs and volume of pharmaceutical treatment. The latter are in turn heavily determined by drug advertising, and especially by the influence of such advertising on persuading prescribers to favour expensive new drugs (even where these offer no clear advantage over older items), to prefer branded items to generic alternatives or to prescribe a drug where none is in fact needed. The expense involved in the advertising itself is also, as indicated by the figures cited above, a significant indirect determinant of the cost of health care.

Finally, the quality of health care will inevitably be adversely affected by any form of dishonesty in advertising that can all too readily lead to the use of inappropriate or unnecessary drug use.

3.2 ADVERTISING, PROMOTION AND MARKETING: SOME DEFINITIONS

The difference between mere advertising and the more expansive process known as promotion is today not particularly well defined – the two are perhaps best seen as concentric spheres. Promotion seems to have been conceived to complement advertising with a series of sales-enhancing tools that may or may not be concerned with the presentation of mere facts (such as the holding of promotional meetings or dinners). It might be said that promotion is more about image-building. Yet most contemporary advertising is also more fundamentally about image-building than the provision of information. We can therefore view promotion as a somewhat more general process, but one that overlaps with advertising.

Images of suffering, prominent in drug advertisements as early as the eighteenth century, have progressively given way to images of the joyful life that one might be expected to attain following treatment. Prior to the withdrawal on safety grounds of the Merck product Vioxx\textsuperscript{R} some of its promotion was built around the portrayal of prominent sporting figures in action, suggesting the drug’s association with a healthy and physically active existence. Testimonials from the nobility and gentry, another tool of the image builder, have changed in style since they first appeared in the nineteenth century but hardly in purpose; in 1999 US Senator Bob Dole featured prominently in the promotion of sildenafil citrate (Viagra\textsuperscript{R})
for the treatment of male erectile dysfunction. It may be too much to hope that the commercial world will ever abandon image-building in its entirety. The risk is however that the poetry, the art and the image readily become so dominant that one begins to wonder whether the information is still there or whether it has become so secondary in the seller’s message that it no longer seems to matter.

Marketing is a concept even wider than that of advertising or promotion and embraces the totality of effort devoted to ensuring that a medicine will be widely and profitably used, extending even to the manipulation of influential parties (Chapter 4) and the astute development of pricing policies (Chapter 6). At its most ambitious, marketing may seek to create a situation in which a medication comes to be regarded as a necessary adjunct to daily living either for the community as a whole or for a distinct population group. Efforts of this type spark massive competition between corporations, each hoping to capture the bulk of a vast new market (see also Section 3.3 below).

3.3 DEFINING STANDARDS AND SETTING LIMITS

As noted in Section 3.2, marketing in its most aggressive form may seek to present a drug as a desirable adjunct to daily living. Such a notion of universal medication featured prominently in a work of fiction, namely Aldous Huxley’s *Brave New World*, published in 1932. In his imaginary world the government had provided the population with wide use of “Soma”, a drug guaranteed to banish concern and dissatisfaction and ensure universal contentment. As Huxley wrote many years later, looking back on his novel:

In the Brave New World the Soma habit was ... the very essence of the Life, Liberty and Pursuit of Happiness guaranteed by the Bill of Rights ... the drug had power to console and compensate, it called up visions of another, better world, it offered hope, strengthened faith and promoted charity ... Soma was not only a vision-producer and a tranquillizer; it was also ... a stimulant of mind and body, a creator of active euphoria as well as of the negative happiness that follows the release from anxiety and tension.\(^\text{12}\)

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Thirty years after the novel had appeared, something remarkably similar was achieved in the real world with the advent of the heavily promoted benzodiazepine tranquillizers. To a large extent they delivered pharmaco-logically the Soma state of universal contentment, and those effects were supplemented by the highly suggestive influence of the advertising that introduced and bolstered them. In 1979 more than 31 million prescriptions for these products were issued through Britain’s National Health Service alone, serving a population of some 56 million, with additional prescriptions being written by private practitioners.

In the meantime, after the oral contraceptives had demonstrated a further (but more genuine) situation in which medicines could be sold to a healthy population and not merely to the ill, the quest to identify or create more such opportunities was intensified. The quest was – perhaps fortunately – not particularly successful. Attempts to persuade older men to turn to androgen supplementation seem to have brought relatively meagre returns. The message that routine oestrogen supplementation was necessary in post-menopausal women (see below) was widely accepted for a time until the adverse effects of the treatment became all too evident. By the end of the century the quest was rampant once more, with the widely disseminated message that every man of middle age now had need of ongoing treatment with a statin to reduce his blood cholesterol. It would be over-optimistic to believe that this will be the last such pursuit of universal medication in which industry will engage.

One might in this connection also mention the prolonged efforts of industry to persuade populations that vitamin supplements are a necessary component of daily living, and the widely deplored efforts of the large firms concerned to silence the whistleblowers and critics who revealed their tactics. Similar is the curious history of “neutraceuticals” – a term coined by Dr Stephen DeFelice at a commercial policy meeting on Lake Como in 1989 to embrace nutrients that one might profitably market as supposedly necessary to ensure a healthy existence. The term has no scientific significance, though agencies and writers have struggled to endow it with one, and it can only be regarded as a commercial ploy. Such tactics must surely be characterized as misleading.

When called upon to defend its advertising practices – and particularly its ambition to “educate” the professions and the public to make wider use of its products – the pharmaceutical industry has been quick to

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advance the argument that illness is commonly under-diagnosed, recognized too late, or treated inadequately. It is entirely true that some conditions go unrecognized too long; type II diabetes in the obese is one case in point, coeliac disease is another. There is also evident undertreatment in much of the developing world because of poverty and lack of services. In wealthy societies, however, these problems are in all likelihood insignificant as compared with those which can result from overmedication, largely engendered by massive promotional pressures. The problem is readily detectable in specific fields; the Royal College of Physicians of Edinburgh, for example, found that both lipid-lowering drugs and agents to lower blood pressure were being much over-used in Britain;¹⁶ overmedication is a commonly recognized problem in the elderly; and there is obvious overmedication where disease mongering (discussed below) has taken a hold. It is much more difficult to assess the extent of overmedication as a whole, since concepts of what constitutes an appropriate level of drug consumption differ from one country to another. Medicine use is considerably more widespread in the south of Europe than in the north. In the United States, the prestigious Centers for Disease Control have described the country as “fatally overmedicated”.¹⁷

The pharmaceutical industry has however spoon-fed journalists with arguments to the contrary, even contradicting authoritative evidence on the matter.

It may not be simple in every field to demonstrate a direct link between the level of promotion and adverse effects on public health, though it is notable that, in some instances, courts handling civil cases have taken account of the likelihood that over-promotion has contributed to injury (see Section 3.8 below). In practice, various other factors are likely to stir governments into action where promotional excesses are concerned. One is the imbalance noted above between the sums currently expended on advertising and those invested in innovative research; a second concern, similarly touched on above, is the increasingly unsustainable expenditure on drugs incurred by publicly funded health systems. A third is the rising incidence and recognition of adverse drug effects. Steps to reduce substantially the industry’s spending on promotion must and surely will be complemented by more extensive measures


¹⁷ CDC (2005), ‘CDC says Americans fatally overmedicated’, Atlanta, GA: Centers for Disease Control.
to monitor the content of advertising and the various other forms of promotion that complement and supplement it.

3.3.1 The Perils of Precipitant Promotion

The risks of reckless promotion have proved greatest when new products are rushed onto a promising market under pressure, either to outrun the competition or to forestall a pending future rival. The first weeks and months of selling may make or break the product’s ultimate career. This is therefore the moment when caution is least likely to be exercised. Yet unhappily it is also the time when caution is most urgently needed. The pre-marketing data on efficacy, safety and appropriate use have yet to be complemented and corrected by data from the field. The regulatory authorities are unlikely to have the capacity – or the experience with the product – to provide prompt and critical surveillance of the introductory promotion. It is not surprising, then, that when one examines the records of the drugs withdrawn from the market for safety reasons within a very few years of their introduction, one tends to find that the promotional materials accompanying their launch have been blemished by errors and exaggeration.

A single example may be given, concerning a cholesterol-lowering drug that ultimately did survive in the market. In 2002 an editorial in the *Lancet* took issue with the launch of rosuvastatin, expressing its concerns in terms as florid as those in which AstraZeneca was promoting the drug in question:

... With no clinical endpoint trial yet completed, the company has chosen to market rosuvastatin by applying adventurous statistics to an over-interpreted syllogism ... Take one example. Stellar was a six-week, open label dose comparison in 2268 patients with primary hypercholesterolaemia ... Astra-Zeneca’s drug was, dose for dose, more effective at achieving national guideline targets for lipid concentrations than its competitors ... Based on these tentative surrogate findings, one Stellar investigator, Peter Jones, commented that, “If I have the option of achieving goals at a lower comparable dose, I would choose that”. This kind of gloss does little to foster sensible, let alone critical, appraisal of weak data. Similar twists in the statistical wind were reported in a promotional supplement to the *American Journal of Cardiology* in March this year by James Blasetto and colleagues ... Blasetto, who works for AstraZeneca in Wilmington, Delaware, combined soft endpoint data from five small 12-week trials to conclude with astonishing certainty that rosuvastatin “can be of considerable value”. It is difficult to understand how such blatant marketing dressed up as research can appear under the name of a respected peer-reviewed medical journal ... Since there are no reliable data about efficacy and safety – and AstraZeneca is facing
unusually acute commercial pressure to force rosuvastatin into the market - doctors should pause before prescribing this drug. Physicians must tell their patients the truth about rosuvastatin - that, compared with its competitors, rosuvastatin has an inferior evidence base supporting its safe use. AstraZeneca has pushed its marketing machine too hard and too fast ... \(^{18}\)

In the ideal world no new drug would be launched precipitately; it would, after the completion of all the due pre-marketing preliminaries, simply be offered calmly and objectively as an alternative to whatever else might be available. From that point onwards it would thrive and prosper or fade into obscurity on its merits and weaknesses alone. That ideal world may for the present be unattainable; but so long as it is not attained, the launch of many a new drug will, alas, be accompanied by the disasters large and small that are the inevitable fruits of commercial impatience.

### 3.3.2 Patterns of Malpractice

It seems all too evident that a pharmaceutical firm that engages in any serious form of malpractice is likely to exhibit a broad pattern of misbehaviour, not limited to a single type of activity. A corporation that breaches accepted norms in the field of advertising may also be found to have conducted fraudulent clinical investigations, withheld important data from the regulatory authorities and failed the community in other ways.

The record $3 billion dollar penalty imposed on GlaxoSmithKline by the US authorities in July 2012 illustrates this fact. Three charges of fraud were involved. They included promoting the off-label use of two anti-depressant drugs (Paxil\(^R\) and Wellbutrin\(^R\)), the withholding of data and the making of unsupported claims for the anti-diabetes drug Avianda\(^R\) and the use by the sales force of inappropriate tactics to get doctors to prescribe their drugs, including various forms of “high-priced entertainment” and large speaking fees.\(^{19}\)

Because sloppiness and recklessness are repeatedly shown to be patterned in this way, we shall in Part III emphasize policy solutions that catalyse holistic reformatory conversations within the cultures of firms.

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3.4 TARGETING THE HEALTH PROFESSIONAL

The bulk of the advertising for prescription drugs is directed, through brochures, medical journals and other channels, at practising physicians and very secondarily at pharmacists and other health professionals. Marketing people are quick to proclaim that this is a critical audience that is itself entirely capable of distinguishing the wheat from the chaff and hardly needs to be protected. One is bound to wonder to what extent that is true; few physicians find the time to examine the claims for every new medicine in detail, virtually none has ready access to the original data and very few indeed have the necessary experience of studying animal and clinical studies; nor does the manner in which the material reaches doctors’ desks render their task of assessing it any easier:

In 2004, a study of the advertising material and marketing brochures sent out by drug companies to general practitioners in Germany concluded that some 94 per cent of the information that they contained had no basis in scientific evidence. About 15 per cent of the brochures did not contain any citations at all, while the citations listed in another 22 per cent could not be found. In the remaining 63 per cent the information was mostly correctly connected with the relevant research articles but did not fairly reflect their results.\textsuperscript{20}

Against this background one must consider some salient aspects of the manner in which the industry has in recent years approached prescribers.

3.4.1 The Detailer

Detailing has a perfectly respectable history. In the early days of twentieth century drug development there was still little in the way of formal continuing education in medicine, and various of the new research-based pharmaceutical corporations realized that if prescribing was to move with the times physicians would need to be taught about new advances; there was often a clear but unmet demand by practitioners themselves for guidance. Teams of young biologists, pharmacists and physicians were progressively recruited and trained for the task by companies like Wellcome in Britain and Organon in the Netherlands. In that way insulin was brought rapidly into everyday use in the 1920s. The educational tradition in detailing was still in evidence with the arrival of the corticosteroids 20 years later, with the new diuretics in the 1950s and

the oral contraceptives in the 1960s.\textsuperscript{21} With increasing competition, however, the educational role tended to become secondary to aggressive selling; detailing became ever more a matter of persuasion by people trained to manipulate the prescriber and themselves manipulated by commercial management.

Driving from one doctor’s surgery to the next with a load of persuasion, the detailer has therefore for at least three generations been regarded by much of the trade as the Big Bertha of drug promotion. The smart blue-suited detailman of the early days has given way to a more informal figure, and the detailing is often enough entrusted to a presentable young woman capable of presenting a seductive sales story. In a sense, we saw an historical shift from a masculine to a feminized sexism in detailing. Printed materials in the form of brochures and journal advertisements play a major role in any publicity campaign, but their texts can be censored and their illustrations criticized by regulators; the detailer, placing himself or herself in front of the doctor’s desk armed with a well-rehearsed presentation and an earnest demeanour but also with well-rehearsed answers to many a question, may drive a sales message home to the individual physician in the way that mere print is unlikely to do. What is more, any misleading statements that they may make and any omissions of which they may be guilty are not likely to come to the notice of the authorities, though sometimes a watchful physician will, when confronted with a dubious story, blow the whistle to the authorities.

AstraZeneca learnt this in 2008. According to an FDA warning letter to the firm, an AstraZeneca sales representative had promoted the company’s antipsychotic Seroquel and Seroquel XL for an unapproved use (major depressive disorder) during an unsolicited sales call to a physician. When the physician requested written information supporting this claim, the company allegedly mailed the physician a list of eight clinical trials supporting the off-label use. Challenged by the FDA, AstraZeneca pointed to a statement in the physician letter that it was not recommending this off-label use; the Agency held however that this disclaimer was insufficient to mitigate the off-label promotion inherent in the original call and in the sending of supportive literature.\textsuperscript{22}

The sometimes less desirable side of detailing may also come to the fore in evidence presented to a court in cases of civil claims for

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\textsuperscript{21} Tausk M (1978), \textit{Organon: De geschiedenis van een bijzondere Nederlandse onderneming} (in Dutch), Nijmegen: Dekker & van der Vegt, p. 348.

drug-induced injury. This was very much the case when Australian patients, who, from 1999 onwards, had suffered cardiovascular harm as a result of taking VioxxR (rofecoxib), brought proceedings against Merck in 2009. As noted in other chapters, public concern regarding the possibility of adverse cardiac effects had been aroused in 2000 and Merck itself had at least by 2001 evidence of a marked increase in heart attacks and strokes. Despite this, the firm’s detailing team in Australia were instructed to create around the product an image of safety and of benefit to the prescriber.

In a statement tendered to the Australian court, Professor Rob Donovan, a professor of behavioural research at Curtin University, described how Merck documents emphasized “the emotional end-benefit for the prescribing doctor”. Merck research had found that older male doctors in particular were “seen as being primarily concerned with providing patient satisfaction”, and wanted “recognition of status by the patient”. VioxxR was portrayed to doctors as a way of gaining the patient’s “recognition of you as a hero”. He described how sales representatives were “rigorously trained ... [to] convey the message there was no increased cardiovascular risk associated with Vioxx”.23

One might add that detailing is today complemented by various other tools of sales promotion. One of these is the practice of “data mining” in which specialized firms gain entry to pharmacy and other records so that the prescribing practice of individual physicians can be examined, and the pattern of detailing adjusted to concentrate efforts on those prescribers who are found to react particularly well to the detailer. Various objections to the practice have been raised, including the breach of the confidentiality that should surround an individual patient’s diagnosis and treatment.24-25

It is revealing to compare these Australian instructions to detailers on selling the VioxxR story to physicians in or around the turn of the century with that same company’s selling techniques 40 years earlier, when a comparable anti-arthritic drug (IndocinR, the brand name of indomethacin) was marketed in the United States. Then, as in 2009, the company’s selling methods were reviewed by a public tribunal, in that case a series

23 Hagan K (2009), ‘Merck told doctors to be “heroes”’, Brisbane Times, 16 April.
of hearings held by the US Senate. Senate investigators found that the instructions to Merck’s sales representatives went far beyond the claims that had been approved by the FDA:

... It is obvious that Indocin will work in that whole host of rheumatic crows and cruds which every general practitioner, internist, and orthopedic surgeon sees every day in his practice ...

Tell 'em again, and again, and again

Tell 'em until they are sold and stay sold.

You’ve told this story now, probably 130 times. The physician, however, has heard it only once. So, go back, and tell it again and again and again and again, until it is indelibly impressed in his mind and he starts—and continues—to prescribe Indocin. Let’s go... Let’s stand on our little old two feet this month and sell the benefits of Indocin.

Take off the kid gloves. If he wants to use aspirin as base line therapy, let him use it. Chances are the patient is already taking aspirin. He has come to the physician because aspirin alone is not affording satisfactory, optimal effects ...

Now every extra bottle of 1,000 Indocin that you sell is worth an extra $2.80 in incentive payments. Go get it. Pile it in ...26

At the time that the Indocin story was being sold, the state of knowledge regarding the drug’s merits and adverse effects was no doubt comparable to what was known about VioxxR at an equivalent moment in its career. For the manner in which Indocin had been introduced, Merck was castigated by its Senate interrogators. One might have hoped that, 40 years later, the corporation would have recalled those events and displayed a little more good sense. Alas ...

3.4.2 Printed Matter

However extensive broader promotional activities may become, the basic text of the data sheet is, as noted above, the objective basis for the assessment of advertising, and any printed material distributed by a firm is supposed to be consistent with it. That applies to direct mail, advertising in the journals, messages on the internet, items in drug compendia and handouts at meetings. It is true that a copy of the entire data sheet, or of its principal elements, is supposed to accompany every

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advertisement addressed to health professionals, but it is likely to appear there in six-point type, readable only for very sharp eyes or with the aid of a magnifying glass; in the case of advertising in the medical journals, the promotional material is likely to be placed between scientific articles, whereas the honest data sheet may be relegated to obscurity in the journal’s back pages. What the reader perusing the advertisement is more likely to read and retain is the main commercial message in emphatic headlines and bright colours. “There is a wind of change in the treatment of arthritis …” was the bold message that launched Lilly’s benoxaprofen (Opren®, Oraflex®) onto the market in and around 1980, with multi-page journal advertising dominated by the promising portrayal of blue skies alongside a declaration that the drug had only “mild and transient side effects”. The “wind of change” headline was clearly intended to suggest that the drug represented a therapeutic breakthrough such as would justify changing to the new treatment. Unhappily, the scientific evidence presented to the authorities did not indicate any such promise; the headline was no more than a speculative extrapolation from some unusual pharmacology, and the latter was destined, after a brief period of marketing in the few countries where it had been approved, to lead too many old people to their deaths and benoxaprofen to the rubbish dump.

3.4.3 Meetings and Symposia

As the commercial rewards of intensive detailing have become more evident, increasing attention has been directed towards particularly influential members of the medical profession – the so-called opinion leaders. The receptive general practitioner may merit an invitation to a dinner meeting or mini-symposium to hear a convincing speaker who has the necessary sympathy with the company’s messages; an opinion leader may expect a trip to Chicago or Hawaii to attend a sponsored symposium, arranged in the context of a scientific conference. Increasing use has also been made of teleconferences to bring together, at least in spirit, those physicians who are already convinced of the merit of a particular treatment and those who, with a little judicious handling, may be persuaded to go along with it. The fact that some manufacturers have over a period of years held promotional symposia in association with professional congresses has met with increasing criticism for blurring the line between science and advertising. It is notable that in 2009 the
American Psychiatric Association voted to discontinue such symposia at its annual meetings.27

Even printed advertising commonly contrives, as we have seen above, to circumvent the shackles imposed by the data sheet. The proceedings at meetings and symposia tend to do this to a much more marked degree since the regulatory authorities are unlikely to be represented in the audience. Talks, visual presentations and handouts are therefore unlikely to reach the eyes or ears of regulatory staff or inspectors. It is not unknown, however, for competitors to infiltrate such proceedings and ensure that any party contravening an industry code is called to order.

3.4.4 Disease Mongering and Scaremongering

*Disease mongering*28 – the technique of persuading the individual that he or she is ill and needs a particular treatment – was thriving in the advertising columns of newspapers in eighteenth century London. By late Victorian times it had in many countries reached an exotic climax with loud full-page advertisements designed to send an alarmed reader hurrying to the nearest drugstore. Such advertising was addressed to the public. In the course of time, however, the promotion of what have been termed “drugs looking for diseases” became similarly prominent in the approach to some branches of the medical profession. Disease mongering may be designed to find a role for a drug for which no very clear field of use has yet been defined, or it may set out to confer on a particular compound an aura of uniqueness and specific purpose that elevates it far above the other members of the pharmacological class to which it belongs.29 In recent decades the technique has been particularly significant in the field of mental phenomena, real or imagined; it is no doubt simpler to create a credible portrait of a particular mental state that may merit concern and call for medication than it is to persuade the prescriber of a hitherto unrecognized physical disorder. As we noted already, most people experience moments of unhappiness, and any individual may at such moments be amenable to the suggestion that he or she is in the grip of a pathological depression. Sadness and grief are very normal reactions to smaller or greater tragedies in the family; stress is a natural reaction to

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a frustrating situation in the workplace; fear is a proper and necessary response to situations in which risk seems close at hand; yet all these conditions, part of normal physiology though they are, can all too easily be portrayed as pathological states calling for drug treatment.

The practice takes two principal forms; the first concerns the need for treatment in well-recognized (but not necessarily pathological) states; the other may amount to creation of essentially fictitious diseases. The two approaches are not always readily distinguished. In the middle of the twentieth century, when the new benzodiazepine tranquilizers and sedatives appeared to provide a safe means of alleviating a wide range of mental states, heavy promotion suggested the need for them to complement any form of specific medicinal treatment, but also in a wide range of everyday situations marked by stress, unrest or sleeplessness. The extreme claim in the heading of the present chapter ("Whatever the indication...Librium") was a component in a sales drive that in the course of a few years created a widespread dependence on tranquilizers as entirely ordinary and helpful crutches in facing the stresses of everyday life:

It is ten years since Librium became available. Ten anxious years of aggravation and demonstration, Cuba and Vietnam, assassination and devaluation, Biafra and Czechoslovakia. Ten turbulent years in which the worldwide climate of anxiety and aggression has given Librium – with its specific calming action and its remarkable safety margin – a unique and still growing role in helping mankind meet the challenge of a changing world.30

Around the same time, manufacturers of simple mouthwashes to relieve bad breath were publicly promoting their use for the treatment of what was now termed "halitosis". Where other conditions are concerned which are not necessarily pathological but have long been presented as such in advertising, disputes have been sowed as to whether one is dealing with genuine disease states necessitating drug treatment or not.

In some instances the selling of drugs for mental conditions in the twentieth century has resulted in reference books on conditions that appear to have had their origin in Madison Avenue rather than Harley Street. The debate as to whether "panic attacks" and "social anxiety disorder" have their roots in psychiatric imbalance or in the creativity of an advertiser has yet to be fought out.31

However prominent the creation of imaginary diseases may have become in the field of mental health, the phenomenon has been by no means absent in internal medicine or gynaecology. The manner in which, from the 1960s onwards, the drug industry succeeded in portraying the menopause – a physiological change experienced by every woman – as comprising the onset of a pathological state, was from the very start astonishing; in due course it was to prove irresponsible – and for some women tragic.

Post-menopausal oestrogen deficiency was first characterized as a disease demanding sustained treatment by two US physicians (Robert and Thelma Wilson) in the 1960s. It had long been recognized that the acute decline in oestrogen in mid-life could produce unpleasant but transitional symptoms calling for relief. What the Wilsons now proclaimed was that, following this brief “climacteric” period, every woman would be left a physiological castrate, deprived of the bodily oestrogens that had hitherto maintained the health of her skeleton, the freshness of her skin and her general health and youthfulness. In Robert Wilson’s book *Feminine Forever*, he essentially proclaimed that with the long-term administration of oestrogens – if necessary for several decades – the miserable decline into old age could be arrested, if not reversed. The original work had been supported by Ayerst, a single manufacturer of oestrogen tablets, but the promise of eternal youth, now proclaimed so emphatically, tempted a series of other hormone manufacturers to exploit with a variety of products what appeared to be a commercial goldmine. The Wilson Foundation was established, with substantial support from the industry, to promote the widespread use of oestrogens following the menopause. Although the idea of long-term oestrogen replacement therapy had not been thoroughly studied, the vast propaganda effort resulted in its rapid acceptance. The resulting gold rush was to last for a little more than a generation during which time it proved exceptionally lucrative; by 1996 an estimated 51 per cent of menopausal women in the United States were receiving oestrogens. By that time, unhappily, it was becoming all too evident that these substances were not in any sense

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physiological for the older women. As early as 1975, the prestigious *New England Journal of Medicine* had published studies showing that post-menopausal oestrogen use greatly increased the risk of developing endometrial cancer; other serious risks emerged as time passed. In 1992 the extensive study of the matter in the framework of the Women's Health Initiative was stopped after pointing firmly to the fact that post-menopausal oestrogen therapy, far from ensuring a guarantee of lasting femininity, brought with it substantial raised risks of breast cancer, stroke and clotting disorders. Although controversy continues, it now appears to be widely agreed that, while a minority of women may have need of appropriate hormone substitution for a time following the menopause, long-term oestrogen replacement therapy on a large scale may well do much more harm than good.36,37

Women have also been the target of disease mongering on other fronts, though not always successfully. Following the worldwide success of products to treat male erectile dysfunction, attempts were made to find a comparably profitable indication in the field of female sexual activity. Teresa Forcades i Vila has documented the manner in which the industry went to work on what became the first mass campaign of illness creation by internet. In 1997, only a few months after Viagra® had appeared on the market, nine pharmaceutical companies planned, organized and financed a meeting of medical specialists in Cape Cod (Massachusetts). Plainly stated, their goal was to create a new pathology (namely “female sexual dysfunction”) in order to suit the economic interests of the pharmaceutical industry. A year and a half later, in October 1998, the first international conference to develop a clinical consensus on female sexual dysfunction took place in Boston, fully financed by eight pharmaceutical companies. Eighteen out of the nineteen authors of the new internationally agreed upon definition had direct economic ties with the companies that financed the event or with other pharmaceutical companies. One year later, in 1999, an article entitled “Sexual dysfunction in the USA: prevalence and predictors” appeared in the *Journal of the American Medical Association (JAMA)*. The authors of the article asserted, with seeming scientific objectivity, that 43 per cent of the American female population was suffering from this “new illness”, an

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illness in fact created and defined to suit the economic interests of the pharmaceutical industry.\textsuperscript{38}

Though the process of disease creation continued, involving biased investigations and further meetings of the interested parties, the venture largely faded from view after the only product ever developed to treat “female sexual dysfunction”, a testosterone patch offered by Proctor & Gamble, was rejected by the FDA in view of the poor quality of the clinical evidence advanced in its support and the risks likely to be involved in its use.

Finally, in this connection, one may note the wave of protest that arose in Canada late in 2012 when Abbott was found to be promoting directly to the public the use of a testosterone gel for the treatment of low testosterone levels in men, which it described as a “common medical condition” that often went undiagnosed. Advertisements were directed at both physicians and the public. Some featured a woman leaning over a man in bed but separated from him by a large block carrying the words “lack of energy” and “low sex drive”. In large type, the advertisement asked whether the reader had “lost that loving feeling” and directed consumers to a website where they were told that low testosterone was common and could be treated with prescription drugs. The reader was told that signs of low testosterone could include “falling asleep after dinner” or “deteriorating work performance”. Health Canada had dismissed complaints against the campaign, but medical experts characterized it as “false advertising” and pointed out that there was little evidence showing testosterone gels had a marked effect on improving sexual satisfaction or depression.\textsuperscript{39} It may also be noted that a testosterone gel study on which a report was published in 2011, involving men aged 65 and older, was stopped early after those treated with the gel experienced higher risks of cardiovascular problems than those treated with a placebo.

\textit{Attention deficit hyperactivity disorder (ADHD)}, a condition supposed to occur primarily in children, merits particularly detailed discussion, since it has been even more violently contested and raises some serious issues of toxicity, dependence and overmedication. It has also raised grave questions regarding the relationship between the pharmaceutical industry, the medical profession and the public.

\textsuperscript{38} Forcades i Vila T (2006), \textit{Crimes and Abuses of the Pharmaceutical Industry}, Barcelona: Cristianisme I Justicia.

It has long been recognized that human beings exhibit a wide degree of variation in their behaviour; those variations may be more pronounced in childhood. One individual is more attentive, more restless, more active or more studious than another; some children and adults are more open to contact and more readily influenced than others. In part these differences may be evident from early childhood, but they are undoubtedly influenced too by the familial and social environment. The community is undoubtedly more colourful and creative and the interaction between individuals more challenging than it would be if all individuals were made in precisely the same mould.

As medicine and psychology have developed, however, they have experienced considerable difficulty in defining the limits of normal variation beyond which an individual must be regarded as sick and in need of support or treatment. The ancient concept of “madness”, clearly related to states of severe mental derangement, was later to be classified under such headings as schizophrenia and manic-depressive psychosis. Lesser deviations from the mean were more puzzling; the old diagnosis of “melancholy” might reflect plain reactive sorrow or a true state of endogenous depression.

As early as 1798 the Scottish physician Crichton described individuals exhibiting what he termed “mental restlessness”. In later years the existence of “learning disabilities” was similarly recognized, and terms such as “minimal brain disorder” were proposed to cover a poorly defined and variable group of difficulties that characterized certain individuals whose behaviour was found troublesome in their immediate circle. In 1902, GF Still defined a similar group of behavioural extremes as comprising a neurological syndrome, and a generation later it was suggested that these conditions might be a consequence of birth injury or of the encephalitis pandemic of the 1920s.

In the United States, the conviction grew that states of impulsivity, hyperactivity and inattention were often seen in association with one another and the American Psychiatric Association (APA) progressively moved to recognize a behavioural state with these general characteristics which it ultimately termed “Attention Deficit Hyperactivity Disorder” (ADHD), listing it under this name from 1987 onwards in its Diagnostic

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and Statistical Manual, the DSM.\textsuperscript{42} It was striking that the definition of ADHD in this US manual was very much broader than in the diagnostic manual issued by WHO. The critical psychiatrist Breggin has examined the background to these developments in the United States, pointing in particular to the fact that in the 1970s the American Psychiatric Association was in severe financial difficulties and sought to overcome these by going into partnership with the pharmaceutical industry. From that point onwards, in Breggin’s analysis, the Association became heavily dependent on industry funding and was strongly influenced by the industry’s policies.\textsuperscript{43} The industry cherished a wish to maintain or expand the sales of psychotropic drugs, including the stimulant amphetamines; the latter were facing strong international pressure to limit or eliminate their use entirely because of their dangerously addictive properties.\textsuperscript{44} One product in this class, the chain substituted amphetamine methylphenidate (Ritalin\textsuperscript{R}) from the Ciba company (a Swiss firm later incorporated into Novartis), had already shown promise in relieving the unwanted behavioural symptoms of individuals believed to be suffering from ADHD, and further clinical trials were actively sponsored. Promotion was undertaken on many fronts including financial support from industry to the parents’ groups organized by families of “ADHD children”, which provided useful lobbying support for wider use of the drug.

In the 1970s it was estimated that as many as 300,000 American children were being treated for ADHD with Ritalin\textsuperscript{R}, and promotion from the Ciba company suggested that some 5 per cent of America’s children might be suffering from the disorder. In 2007 a US study from the Mayo Clinic concluded that among children aged 8–15 the current incidence of the ADHD diagnosis was no less than 8.7 per cent.\textsuperscript{45} Alongside Ritalin\textsuperscript{R} other stimulants and several psychotropic drugs of differing plumage were by this time in use across the country, all backed by advertising.

In some countries the incidence figures published for ADHD are considerably higher than in the United States. In Columbia in 2003 it was estimated that 19.8 per cent of all boys and 12.3 per cent of girls were


\textsuperscript{44} Brecher EM (1972), \textit{Should the Amphetamines be Prohibited?} London: Consumers Union.

suffering from the disorder. European psychologists and physicians have generally been slow – or positively reluctant – to accept that one is dealing with a pathological entity demanding drug treatment; however, under the influence of commercial propaganda, press releases and certain parents’ associations funded by the drug industry, some workers have been persuaded that it is time to “catch up” on the supposed progress made in the United States in this field. A survey in 1999 using the APA’s broad DSM criteria for diagnosis, but applying it to British children aged 5–15, concluded that the national incidence of the disorder was 3.62 per cent among boys and 0.85 per cent among girls.

Bearing in mind that the majority of children with a diagnosis of ADHD – and an unknown but growing proportion of adults – in western society are being treated with drugs, it is relevant to consider their true value for relief of the condition. There is no doubt that where hyperactivity is the dominant complaint, this reacts well in the short term to stimulants such as Ritalin®, but there the certainty ends. Long-term stimulant use in children or into adulthood does not reduce antisocial behaviour; nor do stimulants “produce lasting improvements in aggressiveness, conduct disorder, criminality, education achievement, job functioning, marital relationships or long-term adjustment”, though all these virtues have been claimed for them.

A 2007 review found that there were no good studies of comparative effectiveness between various drugs for ADHD and that there was a lack of reliable evidence on their effects on overall academic performance and

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social behaviour.\textsuperscript{51} There is very little data on the long-term adverse effects or benefits of stimulants for ADHD.\textsuperscript{52}

There is no good reason to consider here whether the state known as ADHD is simply an extreme variation of normal behaviour (perhaps exacerbated by a high sugar diet or precipitated by stresses in the home or at school) or a mental disorder; in either case some form of relief may be called for if the condition is sufficiently disruptive to the normal existence of the individual or his or her family. There is however every reason to express concern about the present state of affairs in several respects.\textsuperscript{53}

First, it is frustrating to find that after 40 years the condition is still so poorly defined that one does not even know whether it is a single recognizable entity or not; in all probability the term covers a very variable cluster of symptoms and characteristics. Commercial selling has grossly oversimplified the picture and the remedy and led to much over-diagnosis and unnecessary treatment.

Second, acceptance to date of ADHD as an entity has led to the extensive use of pharmacological therapy for a condition that, where it truly exists, in all probability will prove responsive to behavioural treatment or perhaps familial adjustment. William Moodie may well have been right when he wrote back in 1947 that "when any ordinary child is unmanageable, the reason is usually faulty relationship between the child and the adult concerned ... it must always be remembered that there are at least two parties concerned".\textsuperscript{54} The imbalance in the choice of treatment is surely attributable in large measure to the simple fact that, while drug use is backed by heavy commercial promotion, behavioural therapy, psychological treatment and family adjustment are not.

Third, very serious concern is merited due to the risks attaching to the principal drugs now in use on a large scale to treat this condition. Amphetamines and some related agents are highly addictive; their nature

\textsuperscript{51} McDonagh MS, K Peterson, T Dana and S Thakurta (2007), 'Drug class review on pharmacologic treatments for ADHD', Portland, Oregon: Oregon Health & Science University.

\textsuperscript{52} King S, S Griffin and Z Hodges (2006), 'A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents', \textit{Hlth. Techno!. Ass.}, 10(23), iii–iv, xiii–146.

\textsuperscript{53} Breggin, \textit{Talking Back to Ritalin}, op. cit.

\textsuperscript{54} Moodie W (1947), \textit{The Doctor and the Difficult Child}, New York: The Commonwealth Fund, pp. 120–22.
encourages misuse and there is a serious high incidence of dependence among patients and other members of their families.

Fourth and finally, the standard of clinical research advanced to justify the exposure of a large population to questionable treatment is highly variable and in some instances abysmal.

A substantial volume of litigation has been brought against the companies concerned, based on grounds such as the above. Now is perhaps the time to turn to other and more rigorous forms of legal intervention. The pharmaceutical industry has here, as in too many other fields, shown its least creditable side, hardly in keeping with its oft-repeated portrayal of itself as an entity that prides itself on having the public interest at heart.

Scaremongering is the only adequate term for the practice of inducing fear and alarm regarding an ailment as a means of promoting the sale of medicines. The technique is an ancient one, which appears to have reached a climax with the emergence of a literate but otherwise relatively undereducated working class in the nineteenth century. Major or minor epidemics proved a rich hunting ground, and if they were lacking there was in fact no need to name the supposed threat at all:

AN ALARMING DISEASE AFFLICTING A NUMEROUS CLASS

The disease commences with a slight derangement of the stomach, but, if neglected, it in time involves the whole frame, embracing the kidneys, liver, pancreas, and, in fact, the entire glandular system, and the afflicted one drags out a miserable existence until death gives relief from suffering.55

Forty years later, the technique was still prominent in advertising. In June 1929 in London, the “Shirley System” was being heavily promoted as a proven remedy for “The Great Epidemic of DEADLY CATARRH”:

Are YOU a victim of this dangerous ailment? If so, don’t neglect it or regard it with indifference, or it may endanger your life ...56

Rather more subtle is the approach adopted in drawing the public’s attention to a range of conditions in which the industry would like to see a greater use of medication in general or of particular products. The worldwide “Healthy Skepticism” movement, based in Australia, has on

55 Opening paragraph of an advertisement for Mother Seigel’s Curative Syrup. Kidderminster Shuttle, 25 June, 1887, p. 3.
various occasions examined the manner in which certain mass media have been employed to engender a progressive growth of concern regarding conditions such as restless legs syndrome, overactive bladder and heartburn. The approach may have become more sophisticated with the years, but it has persisted and become more global. One of the most subtle yet dangerous forms of scaremongering involves the manipulation of facts in order to elicit official and public concern at the highest level regarding a health issue, a particularly prominent manifestation of the technique being the creation of worldwide alarm, among governments, professionals and the public, regarding the supposed swine fever “pandemic” of 2009 (see Chapter 4).

3.4.5 Ghostwriting and Stealth Advertising

Ghostwriting is a favourite tool of the promoter. Like detailing, a certain degree of ghostwriting does on occasion have its uses. Not every talented investigator is fluent with the pen, and it may take some assistance from a professional editor or author to transpose valid scientific results into understandable text. As with detailing, however, an essentially valid tool can be misused.

When the serious adverse effects of the Merck product Vioxx\textsuperscript{R} became known, leading to the drug’s global withdrawal, the Journal of the American Medical Association noted that some of the papers that it had published on the product had been composed by unnamed ghostwriters engaged by the firm. The JAMA editor was reported to have stated to the New York Times that the ghostwriters’ role was not fully disclosed when the papers were published. “I consider that being scammed”, she said.\textsuperscript{58} The author of one of the articles told the Wall Street Journal that ghostwriting was in his opinion “bad science and bad research practice”.\textsuperscript{59} Merck was stated to have declared that the outside authors whose names were on the papers were “intimately involved in the studies”, describing the accusations as false and misleading. The firm however subsequently undertook as part of its settlement of charges to ensure that

\textsuperscript{57} Van Nuland S and Z Damen (2010), Public Information as a Marketing Tool, Utrecht: Healthy Skepticism.


in the future the author to whom a paper was attributed would make a substantial contribution to it.\textsuperscript{60}

A little more adventurously, promotion may involve not merely ghosting an article but ghosting an entire journal. There is a large family of peripheral medical journals with impressive names that at first sight appear to belong to the elite school of peer-reviewed literature, yet are in fact somewhat less chaste. Soberly clad and emanating from prestigious addresses in London, Heidelberg or New York, the content of these "journals of convenience" as they have sometimes been termed are likely to open with a prestigious editorial from a Nobel prize winner or an academician of unquestioned repute. Beyond that, however, their pages are for sale to any address that is prepared to pay a thousand dollars or more for a thousand words. If there is any peer review at all, then it is only a minimal check provided by a supervising editor whose task it is to ensure that the content is sufficiently sober to ensure that the journal, though it may promote some headshaking in academic circles, is not likely to be held up to public ridicule.

Most of the "supplements" published occasionally by the more prestigious journals are in the same class as the journals of convenience. Carrying something of the aura of the peer-reviewed publication whose style and cover they echo, they are, again, accessible to the publicity department of any corporation that can provide both the necessary materials and the equally necessary money. That some prestigious journals prostitute themselves in this way is perhaps explained by the parlous state of their own finances rather than by any belief that their supplements are truly serving the cause of genuine science.

One more phenomenon that merits mention – devoid of merit though it may otherwise be – is the emergent practice which Sheldon Krimsky has termed "stealth advertising". Here is his 2009 account of one such venture, which mobilizes distortion through selectivity rather than falsehood:

... Even the most hardened cynics were left open-mouthed last month by the news that the Australian affiliate of the global drug giant Merck had signed up with publisher Excerpta Medica, a division of Elsevier, to produce a publication with the look and feel of a peer-reviewed journal, yet which contained only reprints of articles, most of them sympathetic towards Merck products. The Australasian Journal of Bone and Joint Medicine was sent to up to 20,000 doctors between 2003 and 2005. The publication had no website and,

\textsuperscript{60} FDA (2008), ‘Merck settles charges of deceptive advertising for Vioxx’, \textit{FDA News Daily Drug Bull.}, 22 May, 5(101).
unlike normal journals, was not open for submissions. Neither was there any
disclosure that it was funded and controlled by Merck. Elsevier has since
revealed that it put out five other industry-sponsored titles between 2000 and
2005 under its Excerpta Medica imprint.\textsuperscript{61}

There is at least one instance on record of a pharmaceutical company
ghostwriting an entire medical textbook. Two prominent authors of a
book published in the United States in 1999, teaching family doctors how
to treat psychiatric disorders, acknowledged in the preface an “un-
restricted educational grant” from SmithKlineBeecham. Documents that
later became available showed however that the company had in fact
been much more closely involved. The grant had paid for a “writing
company” to develop the outline and text for the two named authors; the
company stated that it intended to show three drafts directly to the
pharmaceutical company for comments and “sign-off”, and the page
proofs for “final approval”. Dr David Kessler, a former commissioner of
the FDA, commented: “To ghostwrite an entire textbook is a new level of
chutzpah … It takes your breath away.”\textsuperscript{62}

Practices like this reflect no very great credit on either party. As
Krimsky went on to comment:

This blurring of the boundaries between independently refereed publications
and advertorials is unacceptable. Promotional material should be clearly
marked and easily identifiable. The production of drugs and the production of
reliable knowledge about their safety and use must be kept separate.\textsuperscript{63}

It is impossible to say how much harm practices like this do to patients,
to science, to health or to society, but what is certain is that they do no
good. Drugs are publicized in other indirect and stealthy ways, and
tomorrow they will no doubt be publicized in even more ways. One can
only sigh, and hope that in matters like this society will awaken, come to
its senses, and tolerate these foolish things no longer.

\textsuperscript{61} Krimsky S (2009), ‘Stop these stealth drug adverts’, \textit{New Scientist},
\textbf{202}(2711), 5 June. See also Moynihan R (2009), ‘Merck disguised “marketing
publication” as medical journal to help promote Vioxx, court hears’, \textit{Brit. Med.
J.}, \textbf{338}, 1714.

\textsuperscript{62} Wilson D (2010), ‘Drug maker wrote book under 2 doctors’ names,

\textsuperscript{63} Krimsky, ‘Stop these stealth drug adverts’, op. cit., p. 25.
3.4.6 Sampling and Promotional Trials

The distribution of free samples is a familiar commercial tool to promote sales. In the case of simple consumer products – such as the handing out of samples of cheese or confectionery in a supermarket – there can be no objection to it; it may be regarded as the most honest of all promotional techniques since the recipient can immediately form a personal view of the product and decide whether or not it merits his or her approval. In the case of a typical pharmaceutical product, the immediate impression to be gained from a sample is however unlikely to provide any indication as to whether it serves its proclaimed purpose in treating an ailment or relieving symptoms. For such reasons, most regulatory systems prohibit the sampling of medicines by the public.

Similar considerations are generally considered to apply as regards the handing out of drug samples to physicians, purportedly so that they can form a view on the merits of a product. Bearing in mind the strict criteria which are today considered to apply to a clinical investigation (Chapter 1), the individual doctor's use of samples in the treatment of a number of patients is unlikely to provide any reliable impression as to the value of the drug in question. Similar considerations apply where physicians are invited to examine the effects of the sampled product in their patients and to report back to the company on their findings, the so-called "promotional trial". From the commercial point of view, sampling through a physician is no more than a means of familiarizing the latter with the product so that he may thereafter be more inclined to prescribe it. Although sampling to physicians has been restricted by regulation (e.g. in the United States and elsewhere, the physician must sign a written request for samples before accepting them) and has been discouraged by many medical offices and institutes, it remains a major promotional tool. As the head of a large team of drug representatives in the United States has put it:

The doctors then get to see in the short term whether or not what the pharmaceutical representative and company are claiming is accurate ... Drug sampling gives a drug a presence in the office, so that the doctors' colleagues have access to it. In addition, getting samples in the hands of patients helps doctors help their patients and helps ensure that patients request specific drugs.64

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3.4.7 Off-label Promotion

While it is clear, as noted in the above sections, that companies do in one way or another commonly circumvent various of the limitations inherent in the data sheet, the authorities seem most likely to be spurred into action if a corporation is found to be promoting its product for an indication that has not been approved, and may even have been categorically rejected. Promotion of such "off-label use", which may fairly be regarded as an expression of contempt by industry for the regulatory system and its norms, may offer the prospect of much wider sales than the perhaps niggardly field of use in which the agency considers that the drug’s efficacy and safety have been proven. The temptation to venture into it may prove irresistible:

In 2004 the Pfizer corporation, having acquired the Warner-Lambert company, agreed to plead guilty and pay a sum in excess of $430 million to resolve civil and criminal charges against the latter company. These concerned illegal and fraudulent promotion of NeurontinR (gabapentin) for non-approved uses. The product had been accepted by the FDA only as adjunctive therapy for partial seizures in epileptics. According to the evidence advanced, the firm had promoted the drug for treating bipolar disorder, attention deficit disorder, migraine, seizures resulting from drug or alcohol withdrawal, restless legs syndrome and various other disorders, as well as first-line monotherapy in epilepsy. False or misleading statements had been made to health professionals on these matters, and the company had used persons known as "medical liaisons" who presented themselves, in some cases falsely, as scientific experts in treating particular diseases.65

In October 2005 the US daughter company of Switzerland’s Serono paid $704 million to settle a False Claims Act case involving both civil and criminal allegations. The product concerned was Serostim, a human growth hormone product used to combat AIDS-related physical wasting. Disappointed by the sales achieved for the approved indication, the firm had turned to off-label marketing of the drug, promoting it for supposed loss of body cell mass (diagnosed by an unapproved method) and lipodystrophy.66

In October 2009 Pfizer paid a record $2.3 billion settlement, which included a criminal fine of $1.3 billion, for off-label marketing of its

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product Bextra®. The anti-inflammatory and analgesic product had been approved for relief of common pain and inflammation but was being promoted to relieve acute surgical pain. The product had in the meantime been withdrawn because of an increased risk of heart attacks and stroke as well as the risk of a serious and occasionally fatal skin reaction.67

It seems to be particularly tempting to resort to off-label marketing in the field of mental disorders since many general physicians clearly have difficulty in distinguishing between various conditions; anxiety and depression are for example often mistaken for each other. Persons who are merely miserable – perhaps for very understandable reasons – are readily considered to be suffering from some form of mental imbalance. Advertisers seem only too willing to add to the confusion between one mental disorder and another.

For example, in January 2009 Eli Lilly in the United States paid a total of $1.4 billion to settle civil and criminal charges that it defrauded Medicare and Medicaid by “off-label” marketing of Zyprexa® (olanzapine). This antipsychotic drug had been approved by the FDA for treating schizophrenic or bipolar conditions, but the government alleged that Lilly had widely promoted the use of this drug in nursing home patients to treat dementia, which is not a use approved by the FDA. It may be noted that dementia is not a recognized indication for any antipsychotic drug. $800 million was paid under the False Claims Act and $515 million was a criminal penalty.68 In the same month GlaxoSmithKline was reported to have suffered a $400 million penalty, having falsely promoted its antidepressant Wellbutrin SR® (bupropion) for use in bipolar disorders.69 A comparable case involving AstraZeneca is summarized above (Section 3.4.1).

In many instances where off-label use is challenged, the basis of the complaint is simply a breach of the regulations, with a drug being promoted for an indication in which its efficacy has not been proven. In some cases, however, the off-label use is likely to be positively dangerous

to patients. Anabolic steroids improperly sold to promote appetite and growth in undernourished children\textsuperscript{70} are likely to have permanent virilizing effects. There are unfortunately other examples:

In a study carried out for the Netherlands government into the export activities of Dutch pharmaceutical companies, one firm was found to be selling a combination of an oestrogen and testosterone. The investigators pointed out that there were no known indications for such a combination and that it could have adverse effects, both psychologically and on the genital system.\textsuperscript{71}

From 1997 onwards the Swedish company Pharmacia (later to become a subsidiary of Pfizer) illegally marketed its recombinant human growth hormone product Genotropin\textsuperscript{R} on a large scale as an anti-ageing drug in older adults. As a former vice-president of Pfizer noted: "Pharmacia turned Genotropin into a cash cow by illegally peddling a dangerous drug ...".\textsuperscript{72} The genuine indications for growth hormone are very limited. The company subsequently paid $35 million to settle FDA charges on this score.\textsuperscript{73}

Biotechnology companies, which are relatively new entrants into the pharmaceutical market, have not been slow to engage in the sort of malpractice that older firms have found to be profitable, but nor has the US FDA, despite its limited resources, been slow to track down major abuses. In September 2008, Cephalon, a US biotechnology company, paid $425 million to settle False Claims Act allegations that it engaged in "off-label" marketing of three FDA approved drugs: Actiq\textsuperscript{R} (a narcotic lollipop designed for pain control in cancer patients), Gabitril\textsuperscript{R} (an epilepsy treatment) and Provigil\textsuperscript{R} (a narcolepsy medication).\textsuperscript{74}

It is worth noting that where the FDA agrees to a settlement under a false claims charge it not infrequently insists that the company enter into a Corporate Integrity Agreement under which the Agency will for a predetermined period (e.g. five years) undertake strict scrutiny of its

\textsuperscript{70} Ahmad SR (1990), Bitter Facts about Drugs, Karachi, Pakistan: HAI-Pakistan, pp. 183–4.
\textsuperscript{71} Van Maaren PJM, JWF van Mill and AP Hardon (1994), Dutch Drugs in Developing Countries, Groningen: University of Groningen, p. 45.
\textsuperscript{72} Pringle E (2006), 'Ex-Pfizer VP Peter Rost takes on Goliath', http://www.lawyersandsettlements.com (accessed 3 January 2010).
\textsuperscript{74} HCPro (2008), Pharma Compliance Alert, 1 October 2008.
future marketing practices. The company itself undertakes to appoint a chief compliance officer and a compliance committee to promote and ensure that the firm acts in accordance with its legal obligations. From 2009 onwards, such agreements could include obligations binding on the company’s board of directors. Longer experience with this arrangement (and with what in other countries are called enforceable undertakings) will be needed to determine how effective it is. It is however a procedure that might well be adapted with some learning from the experience so far by regulatory agencies elsewhere (as discussed in Part III).

3.5 THE FOLK ON THE CLAPHAM OMNIBUS

While shopkeepers are accustomed to speaking directly to their customers, pharmaceutical manufacturers are in a different situation. The great bulk of medicines are intended to be selected and employed by the prescriber, whose task it is to recognize and diagnose those conditions in which a particular drug treatment may be called for. It is therefore to the prescriber that promotion will ordinarily be directed. In most countries that is the practice recognized and governed by law and, where there is no relevant law, by longstanding custom and convention.

There are two much-discussed exceptions to this rule. The first of these concerns a limited range of medicines – as a rule long-established products that are relatively simple and safe and that serve for the relief of minor everyday conditions. It is widely agreed that one should not need to have recourse to a doctor for every headache or cold in the nose. The over-the-counter (OTC) drugs that serve these purposes are explicitly listed by many a regulatory agency as eligible for sale without prescription and are labelled in a manner that a lay public can understand.

The second exception that has sometimes been made to the rule that drugs should only be promoted to doctors is more controversial. In New Zealand and the United States it has in recent years been regarded as acceptable for pharmaceutical firms to promote even prescription products to the general public.

Both the above issues merit discussion, because in both fields there are various grades of acceptability. And in both matters one must try to bear in mind the significance of these things for the average person – neither

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brilliant nor stupid, neither learned nor ignorant—"The Man on the Clapham Omnibus", as an English judge put it a century ago.  

3.5.1 "Over-the-Counter" (OTC) Drugs

The self-limiting everyday conditions that can be relieved with OTC medications are as a rule so straightforward and well-recognized that the average consumer will readily be able to determine whether a particular product provides relief or not. If their headache, constipation, diarrhoea, itch or cough is not relieved within a few hours by the medicine they have bought, they will not buy it again. Consumers may on occasion err, but generally speaking they will be as competent in these matters as if they were buying apples and pears.

The range of medicines that are eligible for sale and promotion in this way has varied somewhat over the years as experience in the field with certain newer items (e.g. some anti-inflammatory agents with mild analgesic properties) has reached the point where we can reasonably conclude that they can safely be used in lay hands. The range of indications has also been slightly expanded, and some prescription medicines (e.g. simple agents to relieve diarrhoea) have been released for sale in this way, though sometimes in lower doses than those customarily used by the physician. Codes of advertising practice have also been developed both by regulators and by industry, laying particular emphasis on the limits within which self-medication is permissible and reasonably risk free. The Proprietary Association of Great Britain, as one of the national organizations in this field, requires drafts of advertising material to be submitted in advance for approval by its staff before they are finalized. This requirement actually goes beyond what a governmental authority can demand, since in many countries state censorship in any form is prohibited. The labelling must recommend recourse to the doctor where a condition does not respond promptly or complications appear.

Given the limited potency of most over-the-counter medications and the caution surrounding this field, reckless marketing is rare and risks to public health are generally small. Though even apparently harmless products for external use may cause problems in the very young, the manufacturers generally provide specific warnings. One such product,

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76 Lord Bowen, cited in *McQuire v. Western Morning News Co. Ltd.* [1903] 100 at 109, per Collins MR.

well over a century old, continues to be the subject of new findings. An 18-month-old girl was brought to an emergency department with severe respiratory distress. On questioning her carer, it was found that Vicks Vaporub® had been applied to the area around the nostril for symptoms of an upper respiratory tract infection. She recovered over 24 hours with symptomatic treatment.78 Vicks Vaporub®, an external cold rub containing levomenthol, eucalyptus oil, turpentine oil and camphor, was shown to cause an inflammatory reaction in the airways of the ferret, used as an animal model of human respiratory conditions.79 However, following earlier reports regarding laryngeal spasms caused by inhaled menthol or eucalyptus, the manufacturer had already provided a warning against its use in children under two years of age.

In the United States the situation of drugs on free sale has been complicated by changes in the law brought about, apparently under political and industrial pressure, in the mid-1990s which reclassified a large number of medicines as "dietary supplements", though some of them had pharmacological activity. Products so classified could be sold freely in health stores and were exempt from the regulations applicable to medicines, though controls could be reimposed on individual items where this was considered necessary.

Among the reclassified products were a number of appetite suppressants based on pharmacologically active ephedra analogues. Following deregulation these gained considerable popularity as aids to weight reduction and they were actively promoted in the "alternative" health media. With relaxation in the system of control (including surveillance of manufacturing), some of these products proved to contain widely differing levels of ephedra/epiphedrine analogues, rendering them potentially dangerous to cardiovascular function. Reports of adverse effects, including fatalities, appeared, and the FDA found it necessary to prohibit these products as a group.

One class action was brought in a California case against Cytodyne Technologies, the makers of the ephedra-based product Xenadrine®. The plaintiffs pointed in particular to the advertising claims, which were characterized as false and misleading. The court gave judgment for the plaintiffs and ordered the firm to return $12.5 million in profits on sales

of the product in California over a five-year period, the sum to be deposited in a pool for distribution among the users.\textsuperscript{80}

Some manufacturers took advantage of the liberal regime applicable to "dietary supplements" to market illegal products. "Stiff Nights" was introduced as an "all natural dietary supplement" to "boost sexual stamina, last longer, bed beautiful women" and was stated to be composed of "herbs, mushrooms and greens". In fact it contained sulfadildenafil, a close analogue of the active component of Viagra\textsuperscript{R}, a prescription drug used to treat erectile dysfunction. Following a consumer complaint, the FDA issued a warning in November 2009, pointing out that the product might interact with prescribed nitrates, including nitroglycerine, and cause a dangerous reduction in blood pressure.\textsuperscript{81}

\textit{Promotion to children} is today explicitly prohibited in all the codes and regulations that touch on the subject of drug advertising to the public. This was not always the case. In the past it was not unknown for literature and even samples to be handed out, for example outside schools, as a means of inculcating the medicine-taking habit into a coming generation. From 1889 onwards, the former Thomas Beecham company distributed to primary and elementary schools in Britain a booklet known as Beecham's Help to Scholars,\textsuperscript{82} full of facts and figures for those seeking knowledge. It also prominently displayed claims for Beecham's Powders and Beecham's Pills ("worth a guinea a box").\textsuperscript{83}

In more recent times, some corporations have been accused of approaching a child audience in more subtle ways. In 1994 the British authorities instigated an enquiry into the content of a children's book entitled \textit{Mr Sneeze and his Allergies}, produced in collaboration with an asthma charity, but commissioned by GlaxoSmithKline (GSK). In addition to editorial content, the book contained four pages of allergy advice

\begin{itemize}
\item\textsuperscript{80} Fessenden F (2003), ‘Judge orders ephedra maker to pay back $12.5 million’, \textit{New York Times}, 31 May.
\item\textsuperscript{82} Beecham T (1932), \textit{Beecham's Help to Scholars}, New York: Beechams Pills Ltd.
\item\textsuperscript{83} Note: The composition of Beechams Pills is believed to have changed over the years. In 1909 they were reported to be composed of soap and ginger with a small quantity of aloes; see BMA (1909), ‘Secret remedies’, London: British Medical Association, p. 175. By 1932, 44 million copies of the booklet had been distributed to British schoolchildren. The manufacture of Beechams Pills continued until 1998.
\end{itemize}
from the charity and two pages of promotion for the GSK products Piriton\textsuperscript{R} and Piriteze\textsuperscript{R}. Dr Andrew Herxheimer described the book as "... miseducation, an antieducational move. It is a symptom of something more sinister. This is advertising masquerading as information and education."\textsuperscript{84}

Early in 2010 consumer media in the United States and Canada noted that at least one pharmaceutical firm sponsoring the children’s TV programme Sesame Street on Public Broadcasting (PBS) was exploiting a regulatory provision that permitted non-commercial television to transmit "enhanced underwriter acknowledgements" in which a sponsor might mention its products. The Pfizer corporation followed episodes of Sesame Street with a spot referring to Viagra\textsuperscript{R} (used for erectile dysfunction) and the antibiotic Zithromax\textsuperscript{R} (azithromycin, used in children’s ear infections). Though the spot stated that it was addressed to parents, it was accompanied by images of a zebra and of children playing with a giant toy.\textsuperscript{85,86}

One may also note that some firms have established websites attractive to children;\textsuperscript{87} these are no more acceptable than other attempts to direct pharmaceutical publicity to a child audience. Since the advertising of self-medication remedies to the public can only be considered acceptable in view of the recipient’s ability to exercise a degree of judgement, it cannot be regarded as proper to address such material to children, who inevitably lack the experience and maturity needed to view the matter critically.

### 3.5.2 Direct-to-Consumer (DTC) Advertising of Prescription Drugs

As noted above, this practice is, at the time of writing, officially permitted only in New Zealand and the United States, though it is passively tolerated in a number of developing countries with weak regulatory systems. American TV advertising naturally also penetrates


\textsuperscript{87} See for example everydaykidz.com, sponsored by AstraZeneca.
both Canada and Mexico to a significant extent, and advertising in US journals also has some international influence when these are on sale abroad.

This practice has been under attack even in the two industrialized countries that accept it. DTC advertising is at the date of writing still strictly prohibited in the European Union though pressure from industry to introduce it continues.\(^8^8\) America’s Institute of Medicine urged in 2006 that DTC advertising be restricted during the first two years that a new drug is marketed because some of the health risks of new drugs are not fully documented.\(^8^9\)

Where it is allowed, direct advertising of prescription products to the public can clearly not recommend direct purchase. The reader or viewer can only be advised to consult a physician in the hope of obtaining a prescription for the item concerned. Where even this is prohibited, an advertiser may simply publicize the existence and risks of the relevant illness and recommend a visit to the doctor. The doctor will in the meantime have received promotional material on the advertiser’s product. Despite this circuitous route to a sale, direct-to-consumer advertising produces a massive commercial return, which explains why the industry has placed an ever greater emphasis on it and has been so anxious to secure its acceptance in a larger part of the world. In the United States, company spending on DTC increased twice as fast between 1997 and 2005 as did spending on promotion to physicians (or, for that matter, as did spending on research and development). By 2005, expenditure on advertising to the public attained 58 per cent of the amount spent on promotion to physicians.\(^9^0\) It is clear which activities are today regarded by the US industry as most promising in increasing sales.

Firms have on occasion been ingenious in seeking to defend DTC advertising as comprising news or education rather than publicity. In Australia direct-to-consumer promotion for prescription drugs is prohibited both by law and under the industry’s Code of Conduct. In 2008 the industry association Medicines Australia examined a complaint brought by a physician against the Eli Lilly company. The latter had issued a

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press release to the media regarding its product (Cialis-Once-a-Day®) for treating erectile dysfunction. The text referred to the results of a poll, highlighting a potential increase in the frequency and spontaneity of sex among users of the product. Lilly countered that this was not an advertisement but a news item with factual and educational content regarding a new product. The complaint was upheld, and the Association noted further that the poll in question had been commissioned by Lilly itself and might therefore be viewed as biased. The company was ordered to withdraw the material in question and to pay a fine of AU$60,000.91

In both the Netherlands and Belgium, Novartis marketed a product for the treatment of fungal infections of the nails. In both countries television spots urged individuals with this condition to consult their physicians. Physicians received heavy promotion for the drug in question. At the same time the foundation Hodie Vivere had a publicly accessible website on the internet providing information on fungal nail infections; the website was operated through a server owned by Novartis. Cases against Novartis demanding cessation of these activities were brought by the Ministry of Justice in the Netherlands and by the consumer organization Test Aankoop in Belgium. Both cases were dismissed.92

Although public interest organizations have expressed strong opposition to the proposal to introduce direct-to-consumer advertising of prescription drugs in the European Union, it is not impossible that political considerations will lead to a compromise.

3.6 FEDERAL PRE-EMPTION

In a federal system of government, complications can arise if courts in the constituent states seek to apply stricter standards in cases brought before them than those laid down by federal agencies. In the United States this situation has arisen in some “failure to warn” cases brought against pharmaceutical companies in state courts by patients claiming that they have suffered drug injury. Over a long period, the FDA made no effort to intercede in such cases. In more recent years, however, the FDA has adopted the view that failure-to-warn cases in state-law threaten its ability to protect public health. Adverse rulings might, in the Agency’s view, oblige manufacturers to add warnings that the FDA considered

92 Anon. (2006), ‘Schimmelnagels opnieuw inzet van rechtszaak’ (in Dutch), Dagblad Trouw (Amsterdam), 6 May.
inappropriate; this would place firms in the untenable position of having to violate federal law in order to avoid state damages judgments. The FDA has therefore in the recent past sought to pre-empt such judgments.

The law on this matter will no doubt continue to evolve, but it may be noted that a legal analysis of the problem, published in 2008, argues the case against pre-emption.93 Having regard to the limited capacity of the FDA, but also to the extent to which the detection of adverse drug reactions continues long after a product has been approved and marketed, there would indeed seem to be a case for civil and even criminal courts to accept well-documented charges and claims relating to adverse drug effects not reflected in the original documentation. As the study points out, the current absence of a warning in an approved data sheet or package insert may reflect the fact that an applicant has vigorously opposed it, hence delaying its inclusion.

In principle, an analogous approach might prove justifiable in countries with a unitary structure, particularly where the regulatory system is less effective or less well-resourced than the judicial apparatus.

3.7 THE INTERNET: EVERYBODY’S FRIEND?

As a new phenomenon and tool in commercial society, the internet represents a major challenge to any attempt to set effective advertising standards with the interests of public health in mind. For one thing, the internet is a global entity, the content of which is scarcely amenable to selective control or governance within national borders. For another, it is virtually impossible for the viewer to determine the origin or assess the reliability of material reaching the screen. While it has long been a tradition of responsible print media to separate advertising material from editorial content, it is commonly quite impossible to determine whether material on the internet is authoritative or not and where it originated. Where medicines are concerned, the viewer searching for advice on the effective treatment of a particular condition may well encounter 50 or 100 competing web pages, frequently offering mutually contradictory solutions. Some may be presented on behalf of a reputable and universally recognized source with which the viewer happens to be familiar, such as Doctors without Borders, Britain’s *Drugs and Therapeutics Bulletin* or France’s *Revue Prescrire*. A few may emanate directly from

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named pharmaceutical companies. Many others, however, claim to originate from foundations, societies, university groups or entirely unfamiliar bodies, the standing of which the viewer cannot assess. Of these, a proportion are likely to reflect the commercial message of a particular manufacturer without this provenance being listed or in any way detectable.

The very considerable popularity of various social media has provided yet another channel through which pharmaceutical companies can bring their influence to bear on the public. In July 2010, the United States FDA took its first enforcement action against a pharmaceutical manufacturer for its use of Facebook. The Agency warned Novartis Pharmaceuticals about its advertising and sharing of product information for its leukaemia drug Tasigna through Facebook Share, a social media widget on the Tasigna website. The FDA found that the posted shared content failed to communicate any risk information for Tasigna. The brief statement regarding Tasigna’s use represented a misleading broadening of Tasigna’s indication because it implied that Tasigna could be used to treat a broad group of leukaemic patients rather than the limited subgroup for which its use had been approved. Further, the FDA objected to Novartis’s use of the term “next-generation” to describe Tasigna: “use of this particular terminology was considered to be inherently misleading because it suggested superiority over similar products when no such superiority had been demonstrated by additional evidence or clinical experience”.

In the present state of affairs, therefore, the internet comprises a splendid channel through which valuable information can be provided, but also a dangerous tool for those who present misleading or misguided approaches or who are only too ready to misinform and mislead. To date no satisfactory means has been found of excluding improper and masked promotion from the internet, especially when it emanates from other countries, without impairing the medium’s value in rendering possible the free availability of genuine information. The only effective tool for ensuring that the public are not misled is likely to remain the maintenance of official and public interest sources, recognizable as such, to provide balanced data and counterbalance less desirable input, and educating the public to prefer them.

Retrospective action by an agency is also possible. Some pharmaceutical firms have chosen to present on internet websites “consumer

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information” on areas in which they would wish to encourage drug use, perhaps only hinting at a particular product without mentioning it by name. Where such a presentation is less than objective, the firm may nevertheless be called to account by a regulator. In April 2010, for example, the FDA wrote to Novartis objecting to the content of two websites sponsored by the company that characterized the product Gleevec\textsuperscript{R} (approved only for the treatment of chronic myeloid leukaemia and gastrointestinal/stromal tumours) without mentioning it by name. However the Agency found the texts “false and misleading because they promote the drug for an unapproved use, fail to disclose the risks associated with the use of Gleevec and make unsubstantiated dosing claims” which could “put patients at a higher risk of experiencing adverse events”. The FDA demanded a comprehensive plan of action to “disseminate truthful, non-misleading and complete corrective messages about the issues”\textsuperscript{95}

A particular problem is that of direct sale of drugs through the internet. Sellers in many cases provide no information on their qualifications or affiliations, though some claim to operate from pharmacies and even to work with physicians who can make diagnoses and prescribe medication on the basis of information supplied by an internet user. A very considerable volume of sales has developed through this channel, and it seems likely that a fair proportion of the drugs supplied are either counterfeits having no medicinal value or are different from those ordered. In 2010, the United States FDA warned consumers regarding the risks of buying drugs through the internet. When the Agency itself purchased and analysed several products that were represented online as Tamiflu (oseltamivir), one of the orders, which arrived in an unmarked envelope with a postmark from India, consisted of unlabelled, white tablets. When analysed by FDA, the tablets were found to contain talcum powder and acetaminophen (paracetamol) but no oseltamivir. The FDA was also aware of the experience of a number of people who placed orders over the internet for either Ambien\textsuperscript{R} (zolpidem tartrate), Xanax\textsuperscript{R} (alprazolam), Lexapro\textsuperscript{R} (escitalopram oxalate) or Ativan\textsuperscript{R} (lorazepam). Instead of receiving the drug they had ordered, several customers received products containing what was identified as the antipsychotic drug haloperidol; as a

result, these customers needed emergency medical treatment for symptoms such as difficulty in breathing, muscle spasms and muscle stiffness.96

A number of internet firms, particularly those providing "free" email services, are in fact financed by paid advertising, with the advertisements interspersed between other material. Google found that a proportion of the advertisements that it had accepted emanated from Canadian pharmacy sources, offering to sell drug products to customers in the United States. This practice fell within the ambit of the FDA; and the latter duly threatened to bring criminal proceedings. By August 2011 Google had ceased to accept this drug advertising. It agreed to pay $500 million in full settlement of the charges. Federal investigators stated that the sum represented the firm's revenues from the advertisements and the revenue generated from the sale of the drugs.97

It may be noted that in this case the Justice Department's non-prosecution agreement with Google involved an assertion that the company aided a criminal violation - i.e. that it was an active participant in a crime. While Google was not involved in the actual movement of the drugs, the government viewed its role as sufficiently important to the success of the Canadian pharmacy sales to render its position analogous to that of a body that actually supplied or shipped misbranded drugs. In this case it is also striking that the FDA considered that the chief executive of Google "knew what was going on".98

The Google case could well provide an important precedent when regulatory agencies are faced with advertising contraventions involving the internet, with charges being brought against the domestic arm of the medium employed rather than against the remote offender.

3.8 PROMOTION IN THE DEVELOPING WORLD

Advertising practice and malpractice in developing countries are not essentially different from elsewhere, but the scope for misinformation tends to be greater as a result of weak regulatory systems and the lower level of education enjoyed by much of the population.

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A study by Health Action International Africa’s Kenya office examined 543 print advertisements appearing in five East African countries. Of the brochures distributed at medical facilities, none met the standard criteria as set out by the WHO for ethical advertising of medicines. Only 16 per cent of advertisements released to the general public did so. While all the advertisements listed the brand names of the products concerned, fewer than 40 per cent of them mentioned major precautions associated with the drug or its approved indication. Ten per cent did not even list the active ingredient of the drug. The Deputy Registrar of Kenya’s Pharmacy and Poisons Board was quoted in the same report as stating: “We see so many adverts with so many claims but they are not approved by us ... The penalties are a minimum and the profits people get by advertising far outweigh the penalties.”

A solution may ultimately lie in the current emergence of regional collaboration between regulatory agencies, such as has been established in East Africa and South East Asia, to develop and enforce common standards.

3.9 CONCLUSION: GUIDING AND REGULATING MARKETING

It is clear from the material cited in this chapter that there is a worldwide need for moderation in the practice of pharmaceutical marketing. The examples cited up to this point of regulatory intervention in matters of promotion might tend to suggest that good governance of the process is already largely in place. Indeed, since many countries have both comprehensive regulations on marketing and watchful agencies to enforce them, the physician and the layperson might be tempted to believe that the authorities are able to protect them from falsehoods and half-truths in marketing. The truth, however, is somewhat less rosy. There is much that can be and is being done in the public interest, but the official rules have their weaknesses. We have seen that advertisers are still in many situations capable of using multiple methods for moving around a regulator’s oversight when they wish to do so.

In the Netherlands an ambitious Medicines Act of 1958 established a Board of Control (“Keuringsraad”) for the content of drug advertising. However, the industry and its lawyers promptly pointed out that any form of...

100 Geneesmiddelenwet (1958), Art. 30.
of advance censorship of advertising under the clause in question would conflict with constitutional provisions on the freedom of the press, and the entire clause was therefore never enforced. Retrospective control by the inspectorate was all that proved possible, and in practice a publicity campaign could exert its desired effect before it was censured. When, nearly 50 years later, a university group examined the claims for antihypertensive drugs that were being advanced in a Dutch medical journal, it found that more than a third of the advertisements contained suggestive statements that were not supported by the evidence offered.\textsuperscript{101}

When investigators in Switzerland set out to detect the influence of new national regulations on drug advertising in the major medical journals, they found, disappointingly, that 53 per cent of all the pharmaceutical claims advanced were not supported by the references.\textsuperscript{102} A similar study in Spain examined journal advertising for antihypertensive and lipid-lowering drugs. Forty-four per cent of 125 specific claims assessed were unsupported by the references provided, even where these were taken from seemingly reputable journals.\textsuperscript{103}

With these disappointing findings from three European countries, one turns to the United States to discover what the Federal Food and Drug Administration has been able to achieve. There is no doubt that the Agency has done its best, but with limited resources. A thorough study by the Government Accountability Office in 2006 looked especially at the FDA’s record as regards direct-to-consumer advertising. This is obviously not comparable with the studies in Europe, which examined advertising to physicians, but DTC is a field that the Food and Drug Administration has been watching with particular attention, because of the controversies surrounding it. It seems all too clear that the virulent growth of this form of advertising has outrun the FDA’s ability to keep a consistent watch on it, though the major industries have been sufficiently stingy by critical regulatory letters on the matter to move many of them today to submit voluntarily to the Agency the material intended for use on television and the internet. In 2005, the Agency received in this way 4,600 items relating to direct-to-consumer advertising and 4,690 internet


items. In some instances, prior submission of such material is a condition of settlements with the Agency. In practice, however, the Agency succeeds in reviewing only a small fraction of this advance material or of the advertising actually sent out. Because of the need for prior legal approval of regulatory letters a complaint regarding an advertisement is likely to be delayed for months. In effect this means that if a violation of standards has been detected a considerable time may elapse before it is corrected or punitive action is taken. Between 2002 and 2005 only some eight to eleven regulatory letters yearly were sent to companies, a number that seems to point to the inadequacy of controls rather than the excellence of the advertisements. The most commonly cited violations related to a failure of material to communicate accurately information on the safety of the drug. Distracting visuals in television advertisements were considered to minimize important information on risk. Other letters cited materials for overstating the effectiveness of the drug concerned or advancing misleading comparative claims. The effectiveness of the system over time is also doubtful; firms have tended to react late to regulatory letters and in some cases they have continued the violation complained of or committed it once more at a later date.

In July 2000 the FDA sent a regulatory letter to AstraZeneca Pharmaceuticals regarding a direct mail advertisement for Nolvadex, used in the treatment or prevention of breast cancer. Without additional context the claim regarding the extent of risk reduction obtainable with the drug in women at high risk was considered to be overstated. More than 18 months later a similar regulatory letter had to be sent to the same firm advancing the same objection, this time to a print advertisement.104

Chapter 9 discusses how the internet can be a valuable tool in improving enforcement, just as it is a tool that opens up new paths around the law. The present chapter lays a foundation for both the next chapter on ‘The Art of Manipulation’ and for the discussion in Part III of remedies to strategies of gaming the law. The game-playing mentality is introduced through a new spectrum of marketing innovations that game the law – terms like stealth advertising, advertorials, disease mongering and ghostwriting – that will be joined in subsequent chapters by other variants in the art of law evasion such as evergreening patents. The challenge for regulators is not just the sophistication of the games that are being played with the law and the truth. It is also the sheer quantum of the promotional expenditure – $61,000 per doctor in the 2004

104 GAO, Improvements Needed in FDA’s Oversight of Direct-to-Consumer Advertising, op. cit., p. 33.
systematic US study. This leads us to ask the hard question in Chapter 9 whether this is too much. Is this a massive market failure that costs lives? Should governments consider new taxes on promotional expenditure to dampen it and to fund the regulation of its excesses?

The overriding impression as regards the regulation of drug advertising is that, although a need for critical surveillance exists and despite the existence of adequate criteria to carry out assessment, agencies across the world have too little capacity to police the field more than cursorily. This is one reason we consider options for partial privatization of enforcement of these laws in Part III. In Chapter 10 we will argue that the False Claims Act, used in most of the recent major US cases discussed in this chapter, shows a better way forward for other countries and promises to meet many of the other challenges of pharmaceutical regulation discussed in the chapters that follow.

It is surely unfortunate that, in this area as in others, policy makers are too prone to look at the costs of enforcing adequate surveillance and too little at its benefits. When the GAO submitted its report on the control of DTC advertising in the United States and recommended that additional staff be appointed, it was said that this would be too costly. Bearing in mind the fact that drug firms have continued to trumpet, rightly or wrongly, the benefits of their products in terms of health economics, some serious cost-benefit studies of advertising surveillance could well be justified. Irresponsible advertising can result in truly massive overconsumption of medicines (largely funded from the public purse), and in inappropriate or ineffective treatment resulting in prolongation of illness (and hence economic loss).

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4. The dark art of manipulation: The industry and its puppets

The combined worth of the world’s top five drug companies is twice the combined GDP of all sub-Saharan Africa and their influence on the rules of world trade is many times stronger because they can bring their wealth to bear directly on the levers of western power.

(Julian Borger, ‘Industry that stalks the US corridors of power’, Guardian, 13 February 2001)

4.1 THE ESSENCE OF MANIPULATION

The verb “to manipulate” is used in several senses of which dictionaries duly take note. It is derived from the Latin term manipulus, meaning a handful; the body or object to be manipulated is in other words directly taken in hand in order to influence it. The process may be entirely open and necessary; the engineer, for example, is supposed to manipulate the controls of a machine in order to cause it to operate in an appropriate manner. However, there is also such a thing as covert manipulation; the Concise Oxford Dictionary recognizes this meaning of the term: to manipulate in this sense is to “manage (a person, situation etc.) to one’s own advantage, especially unfairly or unscrupulously”. It is in the latter sense that we use the term in this chapter.

In examining these matters one needs to appreciate that the processes of good governance and honest health care must be open to helpful influences from any quarter. To that end there are consultative committees, hearings and opportunities for lobbying by any relevant party, whether that party represents business, science, the professions or any other interest. The essential element in such provisions is openness; one must know that the lobbying is taking place, the parties involved, the content and the outcome. If that condition is not met and the lobbying is carried out only in the shadows and behind closed doors and if no full

record is published – as is too often the case – one will be unable to ascertain whether the policies that ultimately emerge are truly attuned to the needs and wishes of the community as a whole or have been disproportionately influenced by the pressures exerted by particular parties.

The right to exert pressure in some form is inalienable. The carpenter whose premises are on the High Street may need to exert some persuasive influence on members of the Town Council if that council, with the incidence of traffic accidents in mind, designates the High Street as a pedestrian area, making no provision for the carpenter’s van to bring in timber or to deliver products to customers. The pedestrians’ association or a road safety lobby, on the other hand, may argue firmly for the designation. Democratic society provides in various ways for such representations to be set against one another so that a balanced solution can be found. The essential element in such a situation is clearly the possibility of finding a fair balance between various valid but conflicting interests.

Such traditional approaches to fair governance have in recent centuries continued to function perfectly well where the main concern of governments has been the readily acknowledged interest of the individual, public interest groups or the small trader. The situation is considerably more complex where the parties are not comparable in their size or influence. Massive corporations, having their own agendas and commonly showing intolerance of other interests, were not unknown in the eighteenth century. They became considerably more prominent in the nineteenth and twentieth centuries, and in a field such as pharmaceuticals their size and influence continue to increase. Mergers and acquisitions have accelerated the clout of corporations in recent decades.

A pharmaceutical company is most likely to engage in improper manipulation where it has business interests that do not run entirely parallel to the community’s needs or where the parallel is at least questionable. The entire process of providing sound evidence as a basis for drug approval (see Chapter 1) is commonly handled in an exemplary manner; but it can also involve on occasion the use of presentations by experts whose opinions have been bought or are based on highly selected information that has been fed to them.

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All these processes can be facilitated by a corporation’s manipulation of its own staff to accept and adhere to corporate beliefs, even where they seem to run counter to what an individual employee could well regard as improper. Half a century ago, WH Whyte, who had worked for the Vick Chemical Company, selling over-the-counter pharmaceuticals to American druggists, provided in his book *The Organization Man* a picture of the clone-like conformity of managers in a tightly organized and aggressive company. As Robinson has summarized Whyte’s story, “loyalty was crucial to success, and unorthodox views or behavior ... could be dangerous to career prospects”. In more recent years, a great deal of attention has been devoted to the existence of distinct corporate cultures within individual businesses, though they differ widely in style. The one firm may derive its strength from the strict imposition on staff of a corporate creed, as Whyte experienced it, while another may promote uniform behaviour by fostering a suspicious and even paranoid view of the world outside. Writing in 1988, Jackall indeed portrayed certain managers who had become accustomed to believing that they were somehow under siege, their adversaries including government regulators whom they saw as “brash, young, unkempt hippies in blue jeans who know nothing about the business ...”, to say nothing of unsympathetic consumer activists, government activists and academics. Notions such as these may on occasion help to explain the readiness with which the staff of large corporations engage in unethical behaviour, including the manipulation of society in order to serve corporate interests. This is also why we consider in Part III of the present volume how policies might nurture and create space for the ethical elements of corporate cultures.

It can prove difficult to gather and quantify evidence even of widespread forms of manipulation. A company that for example seeks to influence the public’s opinions or beliefs regarding a particular matter may use various techniques in parallel or in succession, often employing opportunistic outside contractors who come and go and keep no records. If the principal has maintained any records itself, they may well have been discarded.

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In the United States, for example, a grand jury investigation was undertaken into reports that the Ortho Pharmaceutical Corporation, a subsidiary of Johnson & Johnson, had organized a public relations campaign to promote the belief that sun-wrinkled ("photo-aged") skin could be successfully treated, thus restoring a healthy and youthful appearance. The ultimate intention was to promote the use of Ortho’s product Retin-AR, a vitamin A derivative for external use, despite the fact that the drug had some severe adverse effects and had in fact only been approved by the FDA for the treatment of acne. The public manipulation campaign was contracted out to a series of public relations firms. With the grand jury investigation pending, Ortho staff destroyed thousands of documents recording the instructions to the contractors and their subsequent activities. In January 1995, Ortho was fined $5 million and ordered to pay $2.5 million in restitution after pleading guilty to one count of conspiracy, one of obstruction of justice and eight counts of corruptly persuading employees to destroy documents.8

Finally, one must admit that there are often no clear dividing lines between corruption, manipulation and dishonest promotion; all these forms of misbehaviour, dealt with in part in other chapters, can go hand in hand, often overlapping or complementing one another.

4.2 INTERNATIONAL ORGANIZATIONS

4.2.1 The World Health Organization (WHO)

As the health arm of the United Nations, WHO is the most prestigious global organization in its field. Though it is not endowed with legislative authority, WHO has acquired considerable influence throughout the world, reflecting its experience and the expertise available to it. The Constitution of the World Health Organization makes it clear, in its opening article, that the Organization’s goal shall be “the attainment by all peoples of the highest possible level of health”. No other goal is formulated and the membership is composed solely of national governments. All the same, the Constitution lays the basis for the creation of numerous consultative bodies and committees without setting criteria for the eligibility of their members. The swine fever vaccine story, outlined below, raises the question as to whether industrial links at various levels

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have not disproportionately influenced some of the Organization's policies and recommendations. There are other examples of industrial penetration into those WHO programmes that relate in any way to the use of pharmaceutical products. Bodies such as the International Federation of Pharmaceutical Manufacturers' Associations are entitled to attend meetings of the World Health Assembly and the Organization's Regional Committees; they may be invited to speak and on these occasions they are often seen to maintain close contacts with certain national delegations.

As a single instance in which accusations of manipulation at this level have come to the fore, one may take the case of swine fever prevention as it developed during 2009 and the early months of 2010. Not all the elements in the tale are, even today, entirely clear, but the events were overwhelming in their scope, the financial consequences were massive, accusations of improper dealing echoed across the world, and the parties said to have been dishonestly manipulated ranged from WHO itself to the man and woman in the street.

On 11 June 2009 Dr Margaret Chan, the director general of WHO, announced, after what she described as extensive consultation with experts, that the world was about to face a massive influenza pandemic involving the H1N1 ("swine fever") virus. The Organization subsequently upgraded its warning to "risk level 5". A vaccine was already in production on a sufficient scale to meet all anticipated orders. In response, therefore, nations around the world stockpiled vast quantities of the vaccine and of the antiviral products oseltamivir (Tamiflu®) and zanamivir (Relenza®). Typically, as early as April of that year, the Ministry of Health of Norway, a country where the population at the time was only 4.7 million, estimated in the light of data provided by WHO that the disease might result in 13,000 fatalities in Norway alone. Norway duly ordered 9.4 million doses of the relevant products for a total price of $109 million. As a result of such worldwide panic buying, the companies producing the vaccine and drugs made extremely large profits; the investment bank JP Morgan estimated that these ranged from $7-10 billion.

Pandemic alerts are classified by WHO into six phases of severity. Phases 1–3 correlate with preparedness, including capacity development and response planning activities, while phases 4–6 clearly signal the need for response and mitigation efforts.

Summarized from paper by Rachkine VK and K Kluge (2010), 'When swine fever arrived in Europe, WHO stated that mankind as a whole was threatened' (in Norwegian), A-Magasinet.
Even in 2009, however, critics had questioned the WHO prediction and the response to it. During the months that followed the anticipated pandemic indeed failed to materialize. The number of deaths reported globally was hardly greater than the total that had been predicted as likely to occur in Norway alone. By early 2010 uneasy questions were being asked as to the manner in which WHO had drawn its alarmist—and incorrect—conclusion as to an imminent pandemic and the objectivity of those who had advised the director general.

In 2010 the *British Medical Journal* (BMJ) published an investigation into the matter with the Bureau of Investigative Journalism. Their essential conclusion was that WHO’S key decisions were by no means free of commercial influence. Some of the experts advising WHO on the pandemic had declarable financial ties with drug companies that were producing antiviral agents and influenza vaccine. WHO’S guidance on the use of antiviral products in a pandemic had indeed been written by an influenza expert who at the same time was receiving payments for consultancy work and lecturing from Roche, the manufacturer of oseltamivir. Although most of the experts consulted by WHO made no secret of their industry ties in other settings, WHO itself had up to the time of the investigation declined to explain to what extent it knew about these conflicts of interest or how it managed them.

This lack of transparency was compounded by the existence of an “emergency committee”, which advised director general Margaret Chan on when to declare the pandemic – the essential decision that triggered the implementation of costly advance contracts around the world. Remarkably, the names of the 16 committee members were known only to people within WHO. The BMJ investigation noted that both the United States FDA and the European Union’s regulatory body had “struggled” with the paucity of data available to show the effectiveness of the two drug products in question, while the Cochrane Collaboration had stated that on the basis of the available data their effectiveness was impossible to evaluate.

The findings of the BMJ paper tallied with those of other investigations, most notably one undertaken by the Council of Europe, which was

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extremely critical of WHO.\textsuperscript{13} It concluded that the decision-making around the influenza H1N1 crisis had been lacking in transparency. The Council’s Assembly noted that “grave shortcomings have been identified regarding the transparency of decision making processes relating to the pandemic which have generated concerns about the possible influence of the pharmaceutical industry on some of the major decisions relating to the pandemic”.\textsuperscript{14}

WHO’s response to these concerns was characterized by the BMJ as “disappointing”, particularly since there had been an early denial of any industry influence on the scientific advice it had received. The BMJ’s editor compared WHO’s performance unfavourably with the manner in which the Organization had in the past stood up valiantly to industry, for example in the late 1970s when conflicts with industry arose around the marketing of breast milk substitutes and the setting up of the Essential Drugs Programme.\textsuperscript{15}

It is clear that the prediction of epidemics is a difficult and uncertain activity and that honest mistakes can be made; it is also clear that the WHO and governments might similarly have erred had they underestimated a real risk in such a field. In view however of the powerful lobbying influence of the industry with many governments and official bodies and its record on overpromotion, the events relating to swine fever elicited a great deal of critical discussion. Was it not possible that in this case industrial pressure had led to a distortion of public policy, widespread public concern and massive waste?

Infiltration of WHO and its advisory bodies, as in the above case, is not the only means by which the industry has gained influence, sometimes improperly, in the Organization. Judith Richter, a distinguished expert on the role and situation of the private sector, particularly in the field of health, has documented in particular the manner in which the Organization has been readily tempted to augment its sometimes inadequate financial resources by seeking support from a burgeoning private sector.\textsuperscript{16}


\textsuperscript{14} Ibid.


Dr Richter is only one of the commentators who have expressed concern about the consequences of these trends for bodies such as the World Health Organization. As noted at various points in the present volume, the public health sector has grown up and achieved much by being committed exclusively, in its structure and decision-making, to the task of improving the health of the community; it has also attained this situation on the basis of financial and other forms of input from the public sector itself. The private sector, as represented by the pharmaceutical industry, is seen to have a different agenda and to serve the interests of particular groups, notably its investors. In doing so it may very well continue to contribute, as it has in the past, to the creation of new products and solutions to deal with health problems, and thereby provide positive inputs to the public sector, for which it must be duly rewarded. Beyond this point, however, the view appears to be emerging that it is unwise and indeed risky to involve private commerce more closely in the policies and governance of public health; that is all too likely to confuse and divert the clear course that the sector has followed, with striking success, to date.

In 2009 it became apparent that the World Health Organization was in what was termed a "funding crisis". One response to this, from the director general, was to adopt an ambitious "agenda for reform"; among other things this would involve supplementing WHO's existing inter-governmental governing structure by creating a new forum that would bring together various parties including both member states and the private sector. Initially, the Forum was supposed to meet annually, but this plan was abandoned when member states showed a singular lack of enthusiasm for the approach. There had been earlier initiatives to develop more collaboration between the United Nations Organization or WHO on the one side and the business sector on the other, but they had led to expressions of concern on the part of member states.17

In the meantime a number of specific global programmes to promote improved drug development and supply had been developed in which WHO was to participate alongside partners of various plumage, including pharmaceutical companies. These programmes included the Accelerating Access Initiative (to develop treatment of HIV infections and AIDS-related conditions), a Global Alliance for Vaccines and Immunization (GAVI), a similar Global Alliance for tuberculosis drug development and an International AIDS Vaccine Initiative (IAVI). As of 2014 doubt

remained as to the extent to which global alliances would truly catalyse therapeutic progress in their respective fields, but also as to the manner in which any discoveries emerging from these initiatives might best be exploited in the interests of the community generally.

Concerns expressed on his score included those emerging in 2011 when the Dutch vaccine producer Crucell (acquired by Johnson & Johnson) was appointed to the board of GAVI. An independent evaluation commissioned in 2010 concluded that GAVI could have done substantially more to reduce vaccine prices. It was also on record that both Crucell and its predecessor on the board, GlaxoSmithKline, had over a long period refused to stimulate competition by allowing publication of the prices at which they sold vaccines to UNICEF, which bought them on behalf of GAVI. A spokesman for Médecins sans Frontières (MSF) commented that “If you look at the agenda of the board meetings at GAVI, almost all issues impact Crucell’s bottom line”.18

In summary, there is good reason to explore and develop whatever opportunities exist for constructive collaboration between a body such as WHO and the private pharmaceutical sector; but it is an approach that must be pursued with due caution if the interests of public health are not to be compromised.

4.2.2 Other International Bodies

The pharmaceutical industry has over a period of several decades found itself obliged to press its interests in a range of global and regional organizations as their number and influence have developed. In the case of regional bodies accorded drug regulatory authority, the industry’s approach has been similar to that employed when dealing with national regulatory systems. The European Union occupies a special place because of its extensive supranational powers and influence. In the European system, the industry has followed closely the development of centralized and supranational regulations and lobbied for its own interests; in part through its existing links with the authorities in member states and in part by representations to regional consultations and in response to regulatory drafts.

In 2012, a report published by the public interest body, Corporate Europe Observatory, concluded that the pharmaceutical industry was spending some €40 million annually to influence decision-making in the

European Union (EU) – of which nearly half was spent by drug manufacturers on in-house lobbyists. By contrast, civil society organizations, active on EU medicines issues, spent in all only €3.4 million per year. As the authors commented: “With the immense disparity between the affluence of public interest groups and the industrial lobby, it becomes even more difficult to level the policy playing field”. The EU maintains a “transparency register” that is intended to document the sources and extent of lobbying, but entries to the register are purely voluntary and many companies failed to enter a record of their activities: it seemed possible that the true expenditure on pharmaceutical lobbying might amount to as much as €91 million annually. The pharmaceutical industry lobby had been linked to the EU’s move to enhance data protection, which was resulting in delays to marketing cheaper generic medicines; the industry was also implicated in EU member states’ response to the so-called H1N1 influenza pandemic, specifically through mass spending on insufficiently tested vaccines.\footnote{Corporate European Observatory (2012), ‘Divide & conquer: a look behind the scenes of the EU pharmaceutical industry lobby’, available at http://www.corporateeurope.org/sites/default/files/28 March 2012 DivideConquer.pdf (accessed 24 October 2013).}

The participation of the pharmaceutical sector in the World Trade Organization (WTO) similarly merits special consideration. The Organization commenced operation in January 1995 and is intended to supervise and liberalize international trade. From the outset, however, it was charged with the implementation of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which mandates global minimum standards for the protection of intellectual property. TRIPS came into force at the same time as WTO and mandated the extension of patents in all fields of technology, including pharmaceuticals. Pharmaceuticals had up to that time been excluded from patenting in many countries, the view being taken that they were too important to public health to allow private monopolies. That they were now to be guaranteed strengthened patent protection by an enforceable international agreement was largely a consequence of intensive lobbying by a group of western countries, led by the United States, where the pharmaceutical industry had long argued that longer patent protection was necessary if prices were to be maintained at an adequate level to finance productive research. The creation of what were now to be global monopolies for new drugs, resulting in the long-term maintenance of high prices, clearly created a major problem for the populations of developing countries. Expressions of concern at this development came from WHO and the
World Health Assembly, but western countries stood firm with their industries. Ultimately, something of a compromise was reached at the so-called Doha Round of further negotiations in 2001. The compromise reached in the Doha Declaration was that, subject to a number of conditions, a member state was to be entitled to issue compulsory licences on patented drugs so that they could be produced for its domestic market. In this way, a developing country with facilities for domestic production could manufacture generic equivalents of patented products so that the home market could be guaranteed medicines at low cost.

Not surprisingly, the global pharmaceutical industry, which had been strongly opposed to the TRIPS compromise, has since 2001 made strenuous efforts to prevent widespread use of its provisions, and particularly of compulsory licensing. When Thailand in 2005, following a recommendation from the World Bank, issued compulsory licences on several drugs used for the treatment of HIV/AIDS, the brand name versions of which had been prohibitively expensive, the industry inspired an international media campaign that portrayed the Thai government as a pirating military junta that showed no regard for property rights. The Abbott company went so far as to withdraw all new drug applications from the Thai Food and Drug Administration: the result was severe drug deprivation that led to international condemnation from the public health community, non-governmental organizations and AIDS activists.20

The reaction from Abbott and similar attempts by other companies to thwart the application of the TRIPS agreement suggest that the pharmaceutical industry in these matters is still inclined to press its own interests, even at grave cost to deprived populations. The other major strategy has been for the United States, with the European Union following in its wake, to negotiate bilateral trade agreements one by one with significant economies. These bilateral agreements not only consolidate the pharmaceutical industry’s 1995 TRIPS lobbying accomplishments, but extend them.

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4.3 GOVERNMENTS

4.3.1 Industry and Government

At the national level the pharmaceutical industry, as a supplier of products that have a major effect on public health, is often viewed as falling primarily within the field of competence of a Ministry or Department of Health and the various organs associated with it, such as drug regulatory authorities and inspectorates. Critics of the industry therefore tend to the belief that, where corrective action is called for, it is precisely these arms of government and administration that must take up the challenge. In fact this view of the relationship between the industry and government is very incomplete and even misleading. First, it is a fact that Ministries of Health are commonly among the weaker arms of government in terms of both their resources and the authority that they can exercise; they can readily be overridden by others. Second, the pharmaceutical industry has many other links with government that, when conflicts arise, can be more significant than those with the Department of Health. As a major employer in some western countries, the industry can wield a great deal of influence on labour issues; as a potentially important taxpayer, its role in government finance can be substantial; as a commercial entity, it provides vast opportunities for investment by individuals, but also by institutions such as banks and pension funds; as an exporter in many countries, it contributes substantially to the balance of payments and has a patron in the trade ministry; as a processor of chemicals it is likely to have an influence in matters of environmental policy. Within a company, it is these links with authority and sources of influence outside the health field that commonly dominate decision-making where the financial bottom line is concerned and that provide the tools that it can and will employ to manipulate government.

4.3.2 Lobbying

A major figure employed by industry to influence government policies is the lobbyist. The situation in the United States as the twenty-first century dawned, and during the years following, was sketched by Teresa Forcades i Vila: 21

21 Forcades i Vila T (2006), Crimes and Abuses of the Pharmaceutical Industry, Barcelona: Cristianisme i Justicia (emphasis in original).
In 2000, the main pharmaceutical lobby in the USA (PhRMA) counted 297 professional lobbyists, that is, one for each two members of Congress. This number — already vastly exceeding the number of any other lobby — has tripled in recent years. In 2002 PhRMA financed the work of 675 lobbyists, which means that in Washington that year there were more people working to promote the interests of pharmaceutical companies than members of Congress.

PhRMA's principal activities over the years have been to support strong patent regimes, direct-to-consumer drug advertising and various aspects of Medicare reform that benefit the drug industry, while PhRMA lobbying has opposed drug importation and price controls.22 The same body is also known to maintain close contacts with senior government officials overseeing international trade agreements.23

In 2007 PhRMA led the drug industry in lobbying, spending close to $23 million. However, individual firms also undertook direct lobbying in Washington and elsewhere; in that year the biomedical firm Amgen led the field by spending more than $16.2 million, while Pfizer followed up with lobbying expenses of $13.8 million. Independent observers found that these investments had, so far as the companies were concerned, paid off handsomely.24

Marcia Angell has noted that, in 2002, 26 of the 675 pharmaceutical lobbyists on company payrolls were former members of Congress, while 342 were former employees of Congress, 20 of whom had held management roles.25

Lobbying in Washington, DC was complemented by the lobbying of individual state governments. In 2004, the New York Times noted that a group of companies led by Johnson & Johnson had campaigned to convince state officials that a new generation of antipsychotic drugs should replace the cheaper antipsychotic haloperidol (Haldol®); the result was the publication of state guidelines transmitting this message to prescribers. As a consequence, the new compounds became blockbusters

22 Lobby Watch: Center for Public Integrity (2007), 'Pharmaceutical federal lobbying spending flourishes', 2 April, Washington, DC.
23 Ismael MA (2005), 'Exporting prices: drug makers trade group makes the industry's priorities US trade policy', Center for Public Integrity, 7 January.
24 Ismael MA (2008), 'Washington's largest lobby racks up another banner year on Capitol Hill', Center for Public Integrity.
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in their field.\textsuperscript{26} But, as a report commissioned by a consumer group put it in 2009, in line with the literature as a whole:

Newer and quite expensive antipsychotics marketed heavily to doctors and consumers over the past 15 years have largely eclipsed an older generation of drugs developed in the 1950s and 1960s. Research for years appeared to indicate that the newer drugs were better, largely because they had fewer side effects. But other studies now indicate that overall, the older drugs work just as well at a far lower cost.\textsuperscript{27}

On occasion, the interests of a single drug maker on one specific issue may become part of the law as a result of astute lobbying or manipulation in the shadows. A relevant case is cited in Section 4.11 below. The US industry association PhRMA has also where necessary lobbied internationally. In 2005, when the industry was involved in a massive campaign to prevent the importation of lower-cost drugs from Canada, the industry association recruited a former US Ambassador to Canada and his former top aide to lobby Canada’s Departments of Foreign Affairs and International Trade as well as other Agencies that might be able to regulate the cross-border sale of drugs.\textsuperscript{28} PhRMA also sought to convince the public that medicines purchased in Canada might be of poor quality or even counterfeit; in fact this risk only appeared to exist when so-called “Canadian” drugs were purchased through the internet from a dubious source that might not in fact be based in Canada at all; medicines purchased personally in a Canadian pharmacy would in all likelihood be identical with those on sale in the United States.

In other countries with a large domestic pharmaceutical industry, the intensity of lobbying – often conducted by specialized lobbying firms working in close collaboration with producers – is similar. To cite a spokesman for the British Generic Manufacturers’ Association:

\begin{itemize}
\item Ismael MA (2005), ‘PhRMA’s envoys: former ambassador lobbies Canadians on drug imports to US’, Center for Public Integrity, 18 January.
\end{itemize}
Big Pharma in this country uses its muscle in quite a clever way ... They've got the government conned ... No-one ever challenges them. The government buys into the scenario that Big Pharma has to be handled with kid gloves ...29

Lobbying in any country is particularly concentrated on individuals rather than committees or agencies, with an emphasis on politicians and senior administrators who are considered to be in a position to exert influence either in the field of health directly or in economic decision-making. In these fields, governments not infrequently find themselves in a quandary, with health interests seeking something of a restrictive approach to some forms of commercial activity and economic interests favouring an expansive policy.

4.3.3 Direct Interference

On occasion, evidence emerges of more direct interference by the pharmaceutical industry in political acts, with politicians serving as industry's marionettes. When in 2003 the House of Representatives voted to let Americans import less expensive medicines from Canada and Europe, a letter protesting against the measure was made public, bearing the signatures of 53 US Senators. Only later did it emerge that the Pharmaceutical Research and Manufacturers' Association had helped to coordinate the signature campaign.30

Manipulation of government to plead industry's case in international negotiations, even to the detriment of the health interests of foreign populations, has similarly been evident on various occasions, as noted earlier in this chapter.

In the industry's misconceived litigation against the government of South Africa, considered below, it was striking that the United States exerted pressure on the South African government by withholding trade benefits and threatening further trade sanctions.31 The European Union

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similarly joined the US in supporting industry’s case, pressuring South Africa to repeal the legislation.\textsuperscript{32}

4.3.4 Litigation

Only rarely has the pharmaceutical industry as a whole resorted to legal action to challenge a governmental decision. A notable example was the case that 39 pharmaceutical companies brought against the government of South Africa in 1997 for its passage of the Medicines and Related Substances Control Amendment Act, which was designed to make medicines more affordable by allowing parallel imports, enforcing generic substitution and implementing price controls.

Objecting to many of the provisions included in the Act, 39 pharmaceutical companies filed suit to block the legislation. They claimed that the law was unconstitutional and that it violated South Africa’s commitments under the World Trade Organization’s TRIPS agreement. This claim was met with a public outcry against the pharmaceutical industry’s desire to put profits before poor people’s lives. Public protests focused particularly on access to antiretroviral treatment for South Africa’s 4.7 million people living with HIV/AIDS. In spring 2001, when the case went to court in Pretoria, Doctors without Borders (MSF) launched an international petition calling on the companies to drop the case. The petition was widely supported throughout the world by individual signatures and backed by other organizations, while the European Parliament passed a resolution urging the companies to abandon the case, a position echoed by ministers from a number of European governments. Yielding to the powerful combination of public pressure, solid legal arguments and government resolve, the pharmaceutical companies announced that they were unconditionally dropping the lawsuit.\textsuperscript{33}

4.3.5 Developing Countries

Finally, one would stress the fact that an industry which has proved successful in manipulating even the governments of the most powerful countries is likely to be in an even stronger position where the governments of small or developing countries are concerned. A former WHO


official has described a typical instance of influential image-building in an East African country:

When I was with the Minister of Health to advise on pulling together drug policies in Sub-Saharan Africa he asked me to go with him to the Minister of Trade, who was due to have a meeting with this vast pharmaceutical and chemical company X from the States. They turned up with their top brass in the company jet – President, Comptroller and all, to talk about setting up some sort of regional centre here in the capital. You could see from the outset who was in charge, and they knew it. They even knew that my entire country budget for the biennium was ten thousand dollars, and here they were talking in millions and offering to show the Medical College how to train prescribers and fly the Ministers off to see their New Jersey operation. You could see the people at the Government table were bowled over – just deeply impressed, and willing to do more or less anything the company wanted of them.34

In India, evidence has been published showing that doctors were being paid by pharmaceutical companies for each prescription written; in January 2010 it was announced that the Medical Council of India intended to amend its code of conduct for doctors in an attempt to eliminate such abuses.35 The issue of corruption is further considered in Chapter 5.

4.4 REGULATORY AGENCIES

The relationship between pharmaceutical companies and national drug regulatory authorities is commonly reasonable and businesslike. Both parties find it in their interests to maintain it on this footing. Anyone with experience in drug regulation is however likely to have experienced instances in which a restrictive or negative decision has elicited either explicit or barely veiled threats to take the matter to a higher level of government. There are also ways in which firms may signal an intent to explore escalation to a higher authority. In Australia, a way to go, while punishing the bureaucrat who angers them, is to lodge a sweeping “Freedom of Information” request that ties up this bureaucrat in photocopying tens of thousands of pages of relevant government files to send to the company. To put it another way, firms have their own regulatory pyramid of escalated responses (see Chapter 8) for “regulating” the

government. Near the peak of that pyramid, firms can, as Healthy Skepticism alleged to us that one major drug manufacturer did when the British authorities commenced a fraud investigation, threaten to move their British plants to the United States. In countries where corruption exists at the highest levels, the peak of that pyramid can be for the company to bribe the minister to ensure that certain professional civil servants are sidelined (see Chapter 5 on corruption).

A very few such instances of escalation become public knowledge; most remain hidden within confidential regulatory files. When a particular national regulatory body in Europe made it known to the manufacturer of benoxaprofen that it proposed to refuse a sales licence for the drug because of unsatisfactory data as to its safety, the company (Lilly) informed the chairman of the agency that it could not accept the decision and would consider taking up the matter with the Minister of Health. No such attempt to bypass the agency was in fact made, since the drug was shortly afterwards withdrawn from sale worldwide because of the occurrence of fatal hepatic adverse reactions in older patients (see also Section 4.7).

It seems possible that in some instances direct pressure by a firm on agency staff has led to controversial decisions. Lotronex® (alosetron), a 5HT₃ antagonist developed by GlaxoSmithKline and intended for the treatment of irritable bowel syndrome, was approved by the US FDA but withdrawn shortly afterwards, in 2000, because of the occurrence of serious and sometimes fatal gastrointestinal adverse effects. It was then reintroduced in 2002, though with availability and use restricted. In 2001 the editor of the Lancet sharply criticized the FDA for allowing reintroduction; he argued that the treatment of a non-fatal condition could not justify the use of a drug with potentially lethal side effects, and that the FDA should have revoked the original approval for alosetron sooner, when post-marketing surveillance revealed the frequent occurrence of complications. The editor argued that FDA officials were improperly motivated to maintain and reinstate the approval for alosetron because of

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36 This is why the regulator’s regulatory pyramid is best designed collaboratively with representatives of business, consumers and the professions in the room. When the industry and the regulator talk to each other in an open way about how unreasonableness by the one can be responded to with escalation by the other, both sides learn how to make regulation work more cooperatively at the base of the pyramid in the interests of both (and in the interests of the public; see further Chapter 8).

37 Author discussion with a Healthy Skepticism spokesperson.

38 Drost RA (1979), Confidential communication to MNG Dukes.
the extent to which the FDA's Center for Drug Evaluation and Research was funded by user fees paid by pharmaceutical manufacturers, and that the reinstatement of alosetron was negotiated in confidential meetings with representatives of GlaxoSmithKline. Similar views were expressed by others.40

The pressure exerted by pharmaceutical companies on a regulatory agency to attain faster approval of new drugs and a less critical approach to them has been acknowledged by leading regulators, such as Janet Woodcock of the FDA.41 Not uncommonly, the industry also manipulates public opinion to seed the conviction that regulatory stringency and delay are depriving the community of much-needed new drugs; in this way industry may succeed in recruiting a major ally in its attempts to influence policy in its favour.

A former European regulator has described to the present authors how on various occasions, following a critical "hearing" at which a national regulatory body expressed reservations regarding the safety or efficacy of a new drug, the chairman of the agency would be visited privately by a representative of the national manufacturers' association; his pleas for the most liberal possible approach to the product in question, in view of the need for it apparently felt by many patients, clearly led the chairman to press for leniency in the course of further assessment.42

A more structured approach to pressurizing a regulatory agency is that exercised through the political system in countries where the agency does not enjoy a full measure of autonomy. In the United States the 2001 Pulitzer Prize for Investigative Journalism was awarded to David Willman of the Los Angeles Times for the work underlying his paper on the health repercussions of instructions from Congress to the FDA to "work closely with pharmaceutical firms in getting new medicines to market more swiftly". President Bill Clinton had at the same time urged FDA leaders to treat industry as "partners, not adversaries". The authorities themselves imposed an approach more favourable to industrial interests, passing the Prescription Drug User Fee Act of 1992 that accelerated the new drug approval process and the FDA Modernization Act of 1997,

42 Anon. (2012), Confidential representations to MNG Dukes.
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which Marcia Angell later described as "a bundle of gifts to the pharmaceutical industry". The Willman study of the repercussions of these changes, conducted over two years, concluded that "during the ensuing period seven medicines approved after 1993 had to be withdrawn after reports of deaths and severe side effects". In all these cases, the FDA had approved the products "while disregarding danger signs or blunt warnings from its own specialists".

More commonly, pharmaceutical companies provide benefits to regulatory officials through intermediaries, so that the role of the industry is not directly visible and allegations of corruption are evaded. In this sense, the industry also has a tacit pyramid of supports that also includes simple praise of regulators (Chapter 8). The industry thus cleverly integrates carrots and sticks in its manipulation of regulators (and also in its principled resistance to regulatory unreasonableness). In the United States, the Centre for Public Integrity found in 2006 that employees of the Food and Drug Administration had, over the previous eight years, enjoyed travel benefits to the tune of $1.3 million: the funds had been provided by the Drug Information Association which, through its constitution, was closely allied with the pharmaceutical industry.

Some agencies, notably the United States FDA, experience through political channels strong but irregular pressures to amend their policies, at some moments with a view to introducing stricter regulation, at others to achieving a more relaxed approach. The two can alternate. In 1999 two newly approved drugs were quickly withdrawn from the market because of adverse effects; this led to a demand for greater FDA stringency and in 2000 approvals were fewer and assessment times longer. By 2001 this appears to have led to an outpouring of concern from the industry and demands for relaxation. Legislation that modified FDA procedures so as to favour the interests of the industry is known to have been heavily


influenced by industry lobbying, as with the Prescription Drug User Fee Act of 1992 and the FDA Modernization Act of 1997, as mentioned above.

Finally, it would seem that some national regulatory agencies maintain particularly close contacts with pharmaceutical firms within their own borders and may be more favourably disposed to them than to foreign corporations. Such suspicions relating to the French agency were voiced early in 2013. The amphetamine derivative Mediator<sup>R</sup> from the French Servier company was marketed in several countries to treat overweight diabetics. It was never approved in the United States or Great Britain and was withdrawn in Italy and Spain after evidence of injury emerged. It continued to be widely used in France as an appetite suppressant for healthy women and was estimated by the Health Ministry to have killed at least 500 people from heart-valve damage, though other estimates put the death toll close to 2,000, while many more suffered cardiovascular injury. France ultimately withdrew the product and the head of the country’s public health agency resigned. The founder and head of the Servier company was placed under formal investigation on suspicion of manslaughter. A “furore” was reported to have been sparked regarding the lobbying power of pharmaceutical companies in France.<sup>47</sup>

4.5 EDUCATIONAL INSTITUTIONS

Particularly at times when economic growth is slow or the economy is in recession, the educational sector may find itself particularly tempted to accept dominant support from an industrial or commercial source. The firm in question may be acting altruistically or in order to promote some goal of genuinely common interest such as the advancement of basic research or the training of much-needed experts. Where such support is provided by the pharmaceutical industry, it is however not unknown for the latter to exploit the relationship to serve its commercial interest.

In 1999, Dr David Healy, an eminent psychiatrist and researcher holding a university post in Wales, was actively recruited for a professorial post in the Department of Psychiatry and the Centre for Addiction and Mental Health at the University of Toronto, Canada. The position was formally offered to him a year later, in August 2000. In November of that year, with preparations for his move to Canada largely completed, he was invited to lecture at the University of Toronto on a topic related to

<sup>47</sup> Chrisafis A (2013), ‘France shaken by fresh scandal over weight-loss drug linked to deaths’, <i>Guardian</i>, 6 January.
the development of psychiatry in the twenty-first century. His talk was
critical of several aspects of the pharmaceutical industry and its practices,
and it included a comment that the Eli Lilly drug ProzacR (fluoxetine
HCl) and related drugs could lead to suicide, an issue that in Dr Healy's
view should have been studied further. Shortly after Healy's talk, he
received an email from the University retracting his previously offered
position. The reason formally advanced was that his views were incom­
patible with the goals set for further research at the Centre. Healy
concluded however that his job offer was withdrawn because of his
critical views of the pharmaceutical industry and especially Eli Lilly.
Lilly was a significant contributor to the University of Toronto. It
supported 52 per cent of the budget for the Mood and Anxiety Disorder
Clinic that Healy would have headed. In addition it had given a $1.5
million gift to the Centre for Addiction and Mental Health.

In September 2001, Dr Healy filed a lawsuit against the Toronto Centre
and the University of Toronto for $9.4 million in damages and lost
income. In a press conference Healy stated that his greatest concern was
academic freedom and that with some of the damages awarded he would
set up a fund to promote this freedom. The lawsuit was settled out of
court and many of the terms of settlement remain undisclosed. The
University of Toronto has always denied that Dr Healy's dismissal was
influenced in any way by the Lilly funding and there indeed seems to be
no published evidence that Eli Lilly itself threatened to withdraw its
financial support if Dr Healy were appointed; the University however
may have feared that it would lose this source of income if the
appointment proceeded. One might note that in a similar situation
somewhat earlier (in March 2000) the same company had indeed
withdrawn an annual grant of $25,000 to the Hastings Center of
Garrison, New York, which had published in the Hastings Center Report
an article by Dr Healy indicating that ProzacR could induce suicide.

4.6 THE HEALTH PROFESSIONS

The process of aggressive commercial promotion of drugs to physicians,
considered in Chapter 3, at least has the merit of being largely a visible

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48 CBC (2001), 'News and current affairs: the David Healy Affair', CBC
49 Elliot C and T Chambers (2004), Prozac as a Way of Life, Chapel Hill,
and documented process, though even printed advertising directed to the medical profession sometimes drifts away from anything resembling factual information into suggestion and innuendo. Palmlund, in an extensive study of the manner in which physicians were progressively seduced into the belief that oestrogens were a veritable fountain of youth for the older woman, recalls an Ayerst advertisement for PremarinR:

... A beautiful, slim, middle-aged white woman in a glittering elegant evening dress stands under a chandelier with lit candles. One grey-haired gentleman holds one of her hands as if about to kiss it; another seems to give her a compliment. Her smile is radiant and full of charm. The caption says: "help keep her this way".50-51

Somewhere between straight commercial advertising on the one hand (Chapter 3) and frank corruption on the other (Chapter 5) the industry has developed a spectrum of tools to manipulate the physician’s beliefs and practices to its own advantage. Some involve a direct approach; others reach the prescriber’s practice more deviously through “opinion leaders”, professional associations, or any number of selected physicians and pharmacists presenting and publishing views which appear to represent their scientific judgement but which may in fact reflect industrial manipulation. The fact that pharmacists have on the whole been less subject to manipulation than prescribers merely reflects the greater influence of the doctor on the choice of drugs provided to the patient.

4.6.1 The Individual Professional

Many, if not most, firms have over the years made widespread use of “freebies” – small gifts in kind to lubricate the relationship with a prescriber or pharmacist and thereby render the recipient rather more receptive to a message. Even small favours have proved effective in this regard. Whitaker recalls visiting company stalls at the exhibition that accompanied the American Psychiatric Association’s annual meeting in 2008:

Pfizer’s seemed to be the most popular, as the psychiatrists could pick up a new personalized gift each day ... They could also win a gift by playing a video game called the Physician’s Race Challenge, the pace of their virtual

self racing towards the finish line governed by how well they answered questions about the wonders of Geodon® as a treatment for bipolar illness. After playing the game, many lined up to have their photo taken and stamped on a campaign button that said: “Best Doctor on Earth”.52

At a somewhat more serious level, a company may reward a professional—sometimes very generously—for performing a service. In the most favourable case this will have constituted the performance of serious clinical research with an experimental drug; in less creditable instances the physician may be rewarded merely for accepting and using drug samples, for compliance, for attending a meeting or even for providing hospitality.

Various techniques of manipulation have been used over a long period to discourage members of the health professions from publishing unfavourable data, for example regarding the negative outcome of a clinical trial or the recognition of a serious adverse reaction. Half a century ago, the Grünenthal company appears to have succeeded in delaying in various ways recognition of the risks presented by thalidomide to the nervous system or the unborn infant. Editors of journals were discouraged from publishing “anecdotal” reports, and emissaries suggested to physicians that their reputations might be impaired if they were to publish unconfirmed data. A manufacturer may also seek to discourage the prescriber from accepting evidence prejudicial to its drug. One can only guess at the extent of the resultant injury. In the case of Grünenthal and thalidomide (Chapter 1), the influence exerted on prescribers and dispensers was sometimes purely psychological: to cite Sjöström and Nilsson:

The sales promotion men, for their part, were kept busy mounting a front against the doctors and the pharmacists. One salesman wrote: “My happy laughter and appropriate references to the completely harmless properties of the drug were apparently successful in putting the often anxious pharmacists’ minds at rest.”53

A pharmaceutical company is officially prohibited in many countries from recommending that physicians prescribe a drug for indications that have not been approved by the national regulatory agency (“off-label prescribing”) and cases brought against firms for breaching this rule are

repeatedly reported. The matter has already been considered in Chapter 3, but any form of persuasion directed at physicians to engage in this practice clearly constitutes dishonest manipulation of the medical profession. In March 2013, Par Pharmaceutical Companies Inc. pleaded guilty in a federal court at Newark, NJ, to charges of promoting its prescription drug Megace ES\textsuperscript{R} (megestrol acetate) for uses not approved as safe and effective by the Food and Drug Administration and not covered by federal health care programmes. It was sentenced to payments totalling $45 million to resolve its criminal and civil liability in the matter.\textsuperscript{54}

In many parts of the world the industry has found various means of evading the restrictions on therapeutic indications imposed, after consideration of the evidence, by regulatory bodies. In much of the world, for example, physicians regularly receive "drug compendia" that emanate from independent publishers rather than from the regulatory body; the indications listed in such a volume may go well beyond those which the agency regards as acceptable. While it is obvious that the publisher of such a compendium is likely to have received the listing of indications from the manufacturer concerned, this may be difficult to prove. In the United States, where several independent information services exist, an even more extreme situation has arisen. To cite Marcia Angell's account of the position:

Medicaid ... is the largest government program that pays for outpatient drugs. In 1997, Congress named Drugdex Information Service as one of three organizations that would decide which off-label uses Medicaid would cover. Drugdex lists drugs and their uses in a large directory ... Drugdex authorizes about twice as many off-label uses as the two other federally recognized directories ... In 2003 ... they included, for instance, 48 off-label uses for Neurontin, the epilepsy drug. According to the company, Neurontin can be used for hiccups, nicotine withdrawal, migraine, and just about anything else you care to name, and Medicaid has to pay for it.\textsuperscript{55}

In some instances a company can provide a doctor with a financial motive for choosing a particular medicine without making any direct payment; by supplying him or her with free samples that can be prescribed and then charged either to the patient or to the health services it can ensure that the choice of the drug will be simple and profitable.

Finally, the industry has been extraordinarily active in promoting (or infiltrating) educational seminars and courses for the medical profession.

\textsuperscript{54} Editor (2013), 'Par Pharmaceutical pleads guilty', Corporate Crime Reporter, 6 March.

\textsuperscript{55} Angell, The Truth about the Drug Companies, op. cit., pp. 204–5.
In 2008 a working group set up by Britain’s Royal College of Physicians noted that the industry had planted “deep roots” in (and funded half of) postgraduate medical education, sparking concern that continuing professional development programmes had become little more than a form of drug promotion.56

4.6.2 The “Opinion Leader”

The pharmaceutical industry has repeatedly used selected physicians and pharmacists to present and publish views which to the audience appear to represent their scientific judgement, but which in fact may be so one-sided as to constitute industrial propaganda. Some such figures are undoubtedly leaders in their area of expertise; others, having demonstrated their loyalty to a particular firm or product, appear to have had greatness thrust upon them by intensive propaganda. As the Australian physician Jureidini has put it:

Many things undermine good prescribing. Of particular ethical concern is the role of thought leaders or key opinion leaders (KOLs) ... The term KOL is widely used within the pharmaceutical industry ... It seems that industry sees itself as managing we doctors. Not managed in the way that a supervisor instructs a clerk in an office, but managed as an investor manages her portfolio, or perhaps as a spy is managed in a Le Carré novel, without knowing for sure who is in charge and who he is working for. The sad conclusion is that, at least in Australia, almost every prominent psychiatrist is being managed in this way by the pharmaceutical industry. Most KOLs will have had interactions with the pharmaceutical industry that have furthered their career. Most receive at least some current funding from industry ... Of course the individuals involved would likely strongly deny they are being even influenced by industry, let alone managed. But industry documents provide a fairly compelling case that KOLs are closely monitored for return on investment. I am not talking about fraud or corruption; the kind of KOLs I’m talking about are not lining their pockets or even deliberately distorting the data; they are however allowing themselves to be used as a marketing tool by industry.57

One could hardly wish for a more eloquent and accurate portrayal of the manipulative process in this field.

4.6.3 Professional Bodies

The industry has been particularly active in manipulating professional associations. The American Psychiatric Association (APA) is one body that over the years received massive financial support from the pharmaceutical industry. In 2002, the APA's Anand Pandya stated that without pharmaceutical industry funds membership dues could escalate 455 per cent from $540 a year to $3,000. Panya was also president of the National Alliance on Mental Illness (NAMI) which received some 56 per cent of its $12 million-a-year income from drug makers. In July 2008 the US Senate Finance Committee requested that the APA and NAMI provide accounts for all of their pharmaceutical funding. By March 2009, the APA announced that it would phase out pharmaceutical funding of continuing medical education seminars and meals at its conventions. The Citizens Commission on Human Rights International subsequently remarked that, despite this assurance, the APA had within two months accepted more than $1.7 million in pharmaceutical industry funds for its annual conference, held in San Francisco. It is widely considered that the close relationship that grew up between US psychiatrists and the industry was in large measure responsible for much greater use of psychopharmaca in the US than in Europe.

4.6.4 Discrediting Critics

Where even patently libellous statements fail to ensure the manipulation of opinion, a company may, as in the case of an obstructive regulator, seek to engineer more formal means of silencing a medical critic. In 1987 Dr Peter Breggin, who had advanced evidence that psychiatric drugs in essence exerted their effects by disabling the brain, presented his message to a broad audience on the Oprah Winfrey TV show. His comments were so diametrically opposed to those of the American Psychiatric Association, already at that time heavily under the influence of the pharmaceutical industry, that the APA sent a transcript to the National Alliance on Mental Illness, which had similar industry links. The Alliance compliantly filed a complaint with the Maryland State Commission on Medical Discipline, asking it to withdraw Dr Breggin's

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medical licence on the grounds that his statements had caused schizophrenia patients to stop taking their medicines. The Commission wisely declined to take any such action.\textsuperscript{59}

No less discreditable was industry’s response when a lecturer at Harvard University published a book critical of a major antidepressant drug. To quote Whitaker:

In 2000, when Joseph Glenmullen, a clinical instructor in psychiatry at Harvard Medical School, authored \textit{Prozac Backlash}, which detailed the many problems associated with SSRI’s, Eli Lilly mounted a campaign to discredit him. A public-relations firm gathered critical comments from several prominent psychiatrists, who derided Glenmullen as a “nobody” in the field and then mailed these “reviews” to various newspapers. “It’s a dishonest book, it’s manipulative, it’s mischievous” said Harvard Medical School Psychiatrist Jerrold Rosenbaum, even though he was a colleague of Glenmullen’s. The press release naturally did not mention that Rosenbaum was an Eli Lilly consultant.\textsuperscript{60}

\subsection*{4.7 THE MEDIA}

Like many other branches of commerce, the pharmaceutical industry makes every effort to persuade journalists of the correctness and importance of its views, inter alia through the constant supply of press releases, generally composed in such a manner that they are eligible for use as press material without the need for editing. While reputable and major media will sometimes be capable of forming an independent judgement, and will usually be in a position to recognize and discard material that may come from biased or suspect sources, lesser media are more susceptible. Free local newspapers, supported by advertising and working with a minimal editorial staff, are among the media which are relatively willing to accept and publish well-written material that reaches them, without undertaking a thorough review of its content.

At the other extreme, it is not unknown for the industry to inspire massive global campaigns to enlist support when its position appears to be threatened. Such was the response from the pharmaceutical industry when in 2007 the Thai government, making use of its rights under international law as set out in the Doha Declaration (Section 4.2 above), issued compulsory licences for the generic production and sale at low


\textsuperscript{60} Ibid., p. 307.
cost of three essential HIV medicines on which patents were held by western firms. The industry-inspired reaction was summarized by Ellen 't Hoen:

An international media campaign portrayed the Thai government as a pirating military junta that showed no regard for property rights. In a series of editorials, the Wall Street Journal characterized Thailand’s actions as a “seizure of foreign drug patents” and a “frontal attack on property rights” and called those who supported Thailand “anti-patent hooligans” … Ed Silverman, a long-time observer of the pharmaceutical industry, wondered how far the pro-pharma lobby would go in an article ironically entitled “Should the US invade Thailand?”.

Where professional journals are concerned, the industry is in a position to provide massive advertising support to publications adopting and supporting industry’s views or taking the industry’s side when disputes over truth and science arise. Advertising campaigns for particular medicines have on occasion been withdrawn from certain journals expressing critical views, but it is not clear that industry as a whole would withdraw its advertising from a journal. Very occasionally, a journal finds itself threatened with legal action for publishing material critical of a drug product. As the editor of the British Medical Journal recalled in 2003:

One of my first experiences of the relation between medical journals and pharmaceutical companies occurred in the early 1980s after the BMJ had published papers suggesting that a new non-steroidal anti-inflammatory drug, benoxaprofen, might have serious side effects. We were visited by three stern men from Eli Lilly, the makers of the drug – Tony Smith, the deputy editor, conducted the meeting and asked me to join him. The men, whom I remembered (probably wrongly) as having gold teeth, threatened us with legal action, at which point Tony said: “In that case we’ll see you in court.” They backtracked hastily and asked simply to be able to publish a prompt response.

One might add that the drug in question had already, on safety grounds, been refused a marketing licence in the Netherlands and was shortly afterwards withdrawn in Britain after causing numerous fatalities.

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4.8 THE STOCK MARKET

Market manipulation has been defined as “a deliberate attempt to interfere with the free and fair operation of the market and create artificial, false or misleading appearances with respect to the price of, or market for, a security, commodity or currency”. Such manipulation is explicitly forbidden across the world’s legal systems, but the law is not infrequently transgressed. Biotechnology companies, anxious to maintain their share price, have for example been known to present financial analysts with a much more positive view of certain experimental drugs still in the pipeline than that held by their scientific staff.

4.9 PUBLIC OPINION

Advertising to the public, and the limits within which this can be considered acceptable, has been discussed in Chapter 3. In various other ways, however, the pharmaceutical industry can seek to influence public opinion favourably, including the use of the media (see Section 4.7 above) or the internet (Chapter 3), and it may seek to create the impression that the trend has emerged from the public itself. As noted in Section 4.4 above, it can on occasion successfully recruit support from patient or consumer interests in order to strengthen its position vis-à-vis regulatory agencies.

The issue of disease mongering has also been considered in Chapter 3, but many more examples could be cited of the manner in which the lay public has been subtly persuaded over the years to regard mere individual weaknesses as disorders demanding drug treatment. A striking example is the way in which stickers plastered to the walls of bus shelters across the United States induced a large public to regard plain shyness as a pathological state known as “social anxiety disorder”. In all these matters, the industry may make extensive use of public relations firms, as in the case of Ortho’s Retin-A, considered in Section 4.1.

More specifically, a firm may set out to provide financial support to a particular group that might be persuaded to favour its products; women’s groups and clubs seeking speakers have found themselves exposed to propaganda favouring particular forms of contraception, post-menopausal

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64 Robinson, Prescription Games, op. cit., pp. 149–50.
oestrogen treatment or therapy to relieve supposed female sexual hypo-
function. Similarly, industry has funded the creation and programmes of
societies bringing together the parents of children believed to be suffering
from Attention Deficit Hyperactivity Disorder (ADHD, Chapter 3). These
examples are not unique and indeed such practices are widespread.

In September 2000 the Washington Post newspaper reported on the
manner in which Schering-Plough had created a network of state
“hepatitis C coalitions” throughout the United States to build sales of
Rebetron®, the use of which in a single patient would cost $18,000
yearly.65 To cite the report:

Showing all the signs of a thriving grass-roots movement, a host of new
health-care groups are drawing attention to the perils of a contagious,
sometimes lethal virus (infection) called hepatitis C. But contrary to appear­
ances, these coalitions are not spontaneous gatherings of concerned citizens.
They are instead a key part of a carefully orchestrated marketing campaign
funded by Schering-Plough Corp to sell the primary therapy for hepatitis C,
Rebetron ...

Commenting on the above newspaper report, the Center for Media and
Democracy pointed out that, although hepatitis C is potentially life­
threatening, the progress of the disease is very slow, most infected
individuals are unaware of the infection and it may take decades for
symptoms to develop. There is no medical consensus on who should
receive therapy or when they should start. Moreover, if patients were to
buy the two components of Rebetron (interferon and ribavirin) directly
from a compounding pharmacy, they would pay only some $6,000 yearly
for treatment.66

While a firm may in this manner exploit (and even promote) the
existence of consumer groups favouring certain of its products, a group
that appears critical may find itself under vicious attack. In 2013 a
bulletin published by the Netherlands society of cardiac patients (Hart­
patiënten Nederland) reported an interview with a physician (Hans van
der Linde), who drew attention to the fact that certain new antidiabetic
drugs that were not yet marketed could induce pancreatitis and that this
in turn might promote the occurrence of pancreatic malignancy. Although
his views reflected a series of authoritative publications in the British

65 O’Harrow R (2000), ‘Grass roots seeded by drugmaker uses “coalitions”
to sell costly treatment’, Washington Post, 12 September.
The conduct of civil or criminal cases may be deranged in various ways. The most evident is the withholding or destruction of data (Section 4.1) or the provision of false information. On occasion, however, a party may actually act, as it were, behind the court’s back. In September 1989 in Kentucky, the printer Joseph Webecker, who had become psychotic while taking Prozac, took a gun to his workplace and killed eight co-workers, wounding 12 others and then killing himself. There was already evidence that the drug could induce a psychotic state, and civil proceedings were brought against the manufacturer on behalf of the bereaved families. Initially, the plaintiffs began to advance evidence of misbehaviour by the manufacturer (Lilly). At this point, however, the plaintiffs and the manufacturer entered into a secret settlement. To cite a published account:

“Lilly agreed to pay the plaintiffs an undisclosed but huge amount of money” in return for which they agreed not to introduce evidence of Lilly lying to the authorities “nor to pursue a case for punitive damages even if they won the liability phase of the trial. Neither the judge nor the jury were informed of the settlement, and the jury, having heard only a fraction of the incriminating evidence, returned a verdict in favour of Lilly ... When the judge later found out about the secret settlement he moved to change the result from a judgement by jury trial to judgement by settlement.”

The case points to the danger of secret settlements which may be used by corporations to buy a plaintiff’s silence in court and suppress damaging information.

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68 Van der Linde H (2013), ‘Novo Nordisk dreigt patientenvereniging na correcte voorlichting aan hun leden’ (partly in Dutch), email communication to a medical audience, 4 March.
4.11 LEGISLATIVE SUBTERFUGE

Just once in a long while a report appears of criminal interference with the legislative process. One is reminded of a classic case in English law, dating back two centuries, in which a Bill to build an industrial canal was quietly modified before it reached Parliament to include a sentence annulling the marriage of a prominent citizen, a provision that was overlooked by the legislators, the text passed into law and the couple were duly divorced.

In such matters, not a great deal appears to have changed in two centuries. From 1998 onwards there was evidence that the mercurial preservative thiomerosal, used by Lilly and other firms in certain vaccines, might induce autism in children; there was a real risk that the companies might find themselves in due course exposed to litigation. Then, in November 2002, a columnist in the *New York Times* discovered that in the Homeland Security Act, signed by the President in that year, a clause had been inserted protecting Lilly and other firms from litigation relating to injury by thiomerosal;70 cases would be referred to a special "vaccine court". There was a suspicion that the clause had been added to the draft Bill by some person acting on behalf of Lilly, but no member of the Congress admitted to having been involved. By early 2003 moderate politicians of both parties agreed to repeal that particular provision of the Act.71

4.12 CONCLUSION

This chapter has shown that industry manipulation takes endlessly creative forms. In a democracy, undominated dialogue in pursuit of truth is the remedy to manipulation. Aristotle was one of the first to teach us this.72 There are too many manipulators in the world’s pharmaceutical industry for it to be feasible to pursue a policy of using the criminal law


to incarcerate all the manipulators. In Part III, we nevertheless seek to advance a policy that forges a significant role for criminal prosecution of manipulators at the peak of an enforcement pyramid. The idea is to create a space for dialogue that corrects and repairs the harm of manipulation as the more common remedy at the base of the pyramid.

Part III also argues that because public policy must cultivate a less manipulative, less gaming culture in the pharmaceutical industry, and because law enforcement is difficult to sustain on too wide a front (given the skill at gaming law that this book demonstrates), restorative justice at the base of enforcement pyramids has a place. Restorative justice is important when it can lead to Corporate Integrity Agreements that genuinely confront and transform cultures of manipulation. Yet Corporate Integrity Agreements are not at present very searching: they fail to confront corporate cultures of manipulation (Chapters 8–10). To date, they are no more than a tiny step towards crafting a less manipulative industry that respects the spirit of the law in preference to gaming it. This is the reason why Part III takes on the challenge of reforming Corporate Integrity Agreements by embedding them in a more robust framework, comprising tougher hybrid public and private law enforcement, restorative justice and transparent reporting and accountability for corporate integrity that transforms manipulation. The Regulatory Affairs Professionals Society, which serves and develops compliance professionals in the pharmaceutical industry, should play a leadership role here. Corporate ethics and corporate compliance professionalism will be developed in Part III as the best way to flip markets in vice to markets in virtue and to keep manipulative executives out of prison.

5. Corruption, counterfeiting and fraud

Hidden corporate misbehaviour comes to seem normal to those engaged in it. Everyone else is doing it, management seems to encourage it and it takes a brave, or foolhardy, soul to ask: what would happen if the outside world knew what we were getting up to?

(Michael Skapinker, The Financial Times, 2012)\(^1\)

5.1 MONEY AND NEED; DESIRE AND PROMISE

Corruption, counterfeiting and fraud deserve to be discussed alongside one another. In each the emphasis is different, but they constitute a series of practices which overlap and commonly go hand in hand. In either situation the perpetrator is making a deliberate attempt to evade the rules of conduct that society has put in place in order to ensure the honest governance of a complex field.

Medicinal care is one of those areas of human activity in which the temptation to break the rules for the sake of enrichment is particularly strong. Medicines are physically small items that can readily slip through whatever controls on their movement exist; they are goods with a high unit value, meaning that even a little criminal activity can bring a substantial reward; they are also, when viewed superficially, simple items which, unlike a computer or a motor car, can easily be counterfeited; above all they are wanted because they are vital and even life-saving in some situations and lusted for illogically in others. Perhaps above all a temptation to misbehave arises because medicines are the subject of opposed pressures, where massive commercial ambition may find itself thwarted on its impatient way to the market by conscientious professionals and by the exponents of rules and regulations. The commercial urge to circumvent what may seem to some minds to be tiresome obstacles to enterprise will for some prove overwhelming.

5.2 CORRUPTION

5.2.1 Considerations or Bribes?

It would be comforting if one could report that corruption is peculiarly characteristic of those parts of the world where the social conscience is poorly developed and of sectors in which the law has not established clear behavioural norms. However, even in a highly developed society and a sophisticated field of business one does not have to dig deeply to find bribery at work. On occasion small gifts are exchanged as a friendly gesture or hospitality is provided in all innocence, but the borderline between persuasion and corruption is not always sharply defined.

It may be noted that Article 19 of the Code of Practice issued by the Association of the British Pharmaceutical Industry\(^2\) refers to the circumstances in which hospitality can be made available to healthcare professionals and appropriate administrative staff, and the fact that such hospitality must be “subsistence only”. Britain’s Bribery Act of 2010 runs parallel to these provisions, but guidance on the Act issued by the Ministry of Justice speaks more explicitly of “transparent, proportionate and bona fide hospitality and promotional expenditure”.\(^3\)

Enactment of such provisions in the laws of drug-exporting countries may indeed create a clearer view. Examination of the world’s case law during the last two decades unfortunately points to widespread bribery in the pharmaceutical sector and shows that a great deal of commercial practice requires correction. Most major pharmaceutical firms (and many smaller ones) have been found to engage in both corrupt practices and serious fraud, and official concern with corruption and bribery in the pharmaceutical sector has been expressed in both East and West. In China, where blacklisting of firms for improper practices has been introduced in a number of sectors, a revised blacklisting system for pharmaceuticals was introduced in October 2012, one of the grounds specified for blacklisting being “cheating or bribery” in contacts with the authorities.\(^4\) In 2007 the head of the Russian firm Protek was charged with bribery of the health insurance fund FOMS, and officials of the fund

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were charged with accepting its bribes.\(^5\) In Korea, the president of the Korea Pharmaceutical Manufacturers Association, who was also chairman of Ahngook Pharm, was charged in 2009 with having provided illegal kickbacks.\(^6\)

A number of larger pharmaceutical firms today maintain codes of ethics which explicitly reject corrupt practices. The Novartis corporation is a good example of a firm that in 2010 firmly expressed its anti-bribery attitude.\(^7\) Such declarations are welcome and may reflect genuine internal reforms, but they need to be set against repeated reports of corruption in the recent or more distant past. In October 2010 Novartis was fined $422.5 million to settle charges brought against it by the US Department of Justice under the False Claims Act.\(^8,9\) The accusations, a combination of civil liability and criminal charges, related to the epilepsy drug Trileptal\(^R\) (oxcarbazepine) and to the unlawful use of “off-label” marketing. The company agreed to pay a $185 million criminal fine for the off-label marketing charges. The remaining $237.5 million was to resolve civil allegations over the payment of illegal kickbacks to healthcare professionals to prescribe Trileptal and other drugs for off-label use. The complaints, however, dated back more than ten years, during which time the company’s general counsel and executive committee member Thomas Werlen had overhauled the company’s legal function. Interviewed as a whistleblower by the US Department of Health and Human Services in 2006, Dan Abshear, a former sales representative for Novartis during the years 2001–04, described his experience of bribery when working for the firm. To quote from his own account:

I had already worked for two of the top pharmaceutical corporations. The game is the same no matter which pharmaceutical corporation one may work for as a sales representative. That game, as a pharmaceutical representative, is bribing doctors: hiring doctors to be on the payroll of the pharmaceutical


corporation ... the more doctors you acquire in your territory, the more you assure your career with your employer. You are told *ad nauseam* by your employer to seek and pay targeted doctors. With Novartis, they took things a step further: They sent instructions to their sales force to remind doctors paid by representatives that they are obligated to prescribe Novartis pharmaceuti­cals whenever possible. This, of course, potentially clouds the clinical judgments of such doctors, and as a result, adversely affects the restoration of health obligated by the health care provider.¹⁰

### 5.2.2 Bribery of Health Professionals

The extent to which a medicine is used is largely governed by the behaviour of prescribers, and the bribery of a prescriber in its most blatant form involves a direct financial reward for every prescription written – the so-called “kickback”, already touched on briefly in earlier chapters. The firm may itself pay physicians directly, according to the volume of their prescribing, or it may provide them with gratuitous samples which they can prescribe, claiming payment of the normal price by the patient, by the health services, or by an insurer.

In 2013, figures compiled by a consultancy for the *Financial Times* showed that some 12 leading drug companies had paid US doctors a total of more than a billion dollars during the previous calendar year. At the time, the industry was under no obligation to disclose such payments and data on payments made by some major firms were therefore lacking. So-called “sunshine legislation” was due to come into force in 2013–14 and would provide a fuller overview of transactions, but even with the figures now available critics pointed to the fact that such spending could unduly influence physicians and their prescribing patterns.¹¹

Corruption of physicians is sometimes only part of a chain of related and potentially injurious forms of malpractice. To cite a newspaper report in Britain, commenting in 2012 on the imposition of a $3 billion fine on GlaxoSmithKline in the United States:

> How can we doubt a company that announces as its priorities “improving the health and wellbeing of people around the world” and “being open and honest in everything we do?” Now GSK admits that, in effect, it risked damaging the health of people around the world, and was secretive and fraudulent in some


of what it did. Among other things, it suppressed scientific studies that didn’t suit ... and overhyped others that did. It also hosted outings for doctors in exotic locations and showered them with perks, knowing that this would boost prescriptions of its drugs.¹²

Nor is it entirely surprising that in the United States, proven cases involving kickbacks to physicians have frequently gone hand in hand with evidence that the firms concerned had also systematically defrauded the publicly financed Medicare and Medicaid systems. In October 2001, TAP Pharmaceutical Products paid $559 million to resolve False Claims Act allegations that it illegally gave kickbacks to doctors. It was alleged to have provided free samples of its products on the understanding that doctors would bill Medicare and Medicaid $500 per dose. In 2007, Bristol-Myers Squibb (BMS) and its subsidiary Apothecon Inc. paid more than $515 million to settle False Claims Act allegations that it paid kickbacks, promoted off-label uses and violated Medicaid’s “Best Price” statute.¹³

In June 2007, the New York Times reported that psychiatrists in Vermont and Minnesota topped the list of doctors receiving pharmaceutical company gifts (rising fivefold over a six-year period) and that this relationship corresponded to the growing use of atypical antipsychotic drugs in children.¹⁴ In February 2008, Merck paid $671 million to resolve charges under the False Claims Act that it failed to pay proper rebates to Medicaid under the Best Price Statute and that it paid kickbacks to physicians for prescribing its drugs ZocorR (simvastatin), VioxxR (rofecoxib) and PepcidR (famotidine). The whistleblowers who exposed these practices to the authorities were to receive more than $115 million of the sum paid.¹⁵

These few examples, taken over a seven-year period (and others from a range of countries as cited elsewhere in this volume), point to the failure of substantial fines to dissuade supposedly reputable corporations from a known form of improper and illegal behaviour, in essence constituting

¹³ Note: The US “best price” statute now requires a pharmaceutical company to give the public Medicaid system the same discount that it allows to its best customers.
both corruption of the medical profession and theft from the public purse. Such malpractice is not exclusive to a particular social or political system. In September 2013, shares in the Chinese firm Sino Biopharmaceutical were reported to have fallen greatly in value after state TV broadcasts claimed that the company had bribed doctors with overseas trips to Thailand and Taiwan.16

Various countries now have specific legislation prohibiting physicians from accepting bribes. Analogous rulemaking by the medical profession was announced in India in 2010,17 but it is yet to be seen how effective this and similar measures will prove to be in eliminating malpractice.

5.2.3 Regulation and Inspection

In a situation in which a degree of control over the activities of a powerful industry is entrusted to civil servants and academics, who may be receiving only relatively modest salaries, it is not surprising that the latter are on occasion suspected of corruption. A particularly striking instance of proven corruption in the regulatory sector emerged in Italy in 1993.

Professor Duilio Poggiolini was appointed director general of Italy’s Pharmaceutical Services in 1973. In that capacity he dealt with both drug registration and pricing and he represented Italy in scientific organs of the World Health Organization and the European Community. In 1991 he was elected chairman of the European Community’s Committee for Proprietary Medicinal Products (CPMP). On 20 September 1993 he was arrested in Lausanne, Switzerland, on charges of forgery and bribery in the course of his official work in Italy. The charges related to his having received sums of money from large pharmaceutical companies for permitting price increases on certain drugs and for favouring the registration of certain products as well as their eligibility for remuneration. At the time of his arrest, a sum of 15 billion lira was found in a Swiss account in the name of his wife Maria; a search of his Swiss villa revealed a number of hidden items, including gold and silver ingots, rare and antique coins, gold objects, jewels and precious stones. Various pharmaceutical companies were named in connection with his acquisition of wealth. After a period of preventive detention, Professor Poggiolini was sentenced in 2000 to seven and a half years in prison and his wife to

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17 MIMS (2010), ‘Indian Medical Council defines do’s and don’t’s for doctors’, Monthly Index of Medical Specialities (India), New Delhi, 31 January.
four years for complicity. The sentences were subsequently reduced, but a substantial part of his wealth was confiscated. In April 2012, Italy’s Supreme Court laid down a final ruling confirming a judgment of the Court of Auditors of April 2011, fining Poggiolini 5,164,569 euros to compensate the state for offences of corruption or bribery in that the accused “in the years 1982–1992, respectively, in positions covered under the government, had received money from several pharmaceutical companies, resulting in a loss of revenue derived from the unjustified rise of total pharmaceutical expenditure”.

Even 15 years after the original revelations, it seemed doubtful whether consistent improvement had been achieved in Rome. In May 2008 a senior official of the Italian Agency, Pasqualino Rossi, was arrested on corruption charges; a month later Dr Poggiolini’s successor, Nello Martini, was similarly taken into custody. The charges, which followed lengthy police investigations with wiretaps and hidden cameras, specifically involved alleged payments by both Glaxo and Bayer. Both companies denied involvement.

Unfortunately, one might add, other cases of this type are not unknown, even in very different parts of the world. In February 2008, the senior drug controller in the Indian Himalayan state of Himachal was arrested by police while going the rounds of pharmaceutical companies in a borrowed car to collect bribes from them. According to an Indian news agency report issued in July 2012:

In May, when a Parliamentary panel, during a routine examination of healthcare regulatory bodies, alleged corruption in the approval of new drugs, it was merely pointing out one symptom. Such symptoms pervade the entire

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21 Silverman E (2008), ‘Bayer & Glaxo linked to bribes in Italy’, Pharma Blog, 23 May.
drug regulation landscape, which is made up of many entities, each one with its own set of shortcomings and conflicts.\textsuperscript{24}

The Head of China's State Food and Drug Administration (SFDA), Zheng Xiaoyu, who retired in 2005, was arrested 18 months later and charged with gross corruption; it emerged that he and his family had taken bribes of at least 5.5 million yuan (£357,000) from certain Chinese pharmaceutical companies to approve their medicines. Among the drugs he was accused of approving was glycerol contaminated with diethylene glycol, a compound that had led to deaths in other countries (see Chapter 1). Two other members of the SFDA staff were also arrested and charged with accepting bribes.\textsuperscript{25} Zheng Xiaoyu was condemned and he was executed by lethal injection in July 2007.\textsuperscript{26,27}

Again in China, apparently as a consequence of the new procedures to counter "cheating and bribery" in contacts with the authorities,\textsuperscript{28} much evidence of criminal malpractice was reported to have emerged, involving both Chinese and western companies. In July 2013, China's Public Security Bureau published a statement accusing GlaxoSmithKline of involvement in a massive scheme to raise drug prices in China by bribing doctors and government officials in three cities. The company claimed that an internal investigation had turned up no evidence of wrongdoing, but the authorities were said to have placed at least 30 GSK employees, including a number of executives, under house arrest and constant surveillance.\textsuperscript{29}

The international media subsequently reported that the payment of bribes by pharmaceutical firms in China had become a matter of "routine".\textsuperscript{30} According to one western report, the British manager of

\textsuperscript{26} Anon. (2007), 'Former head of China's drug watchdog executed', Xinhua News Agency, 10 July.
\textsuperscript{27} Jia, 'Bribery and corruption dog China's drug business', op. cit.
\textsuperscript{28} Zhu, 'New blacklist system in the field of pharmaceutical security', op. cit.
\textsuperscript{29} Daily Telegraph (2013), 'Top Chinese official targets GSK in bribery probe', Telegraph Media Group, 11 July.
\textsuperscript{30} Patience M (2013), 'Bribery “routine” for foreign pharmaceutical firms in China', BBC News, 12 August.
GlaxoSmithKline (GSK) China had fled the country and four senior executives from the company were being held by Chinese police on suspicion of having committed what the authorities termed "serious economic crimes". The suspects were believed to have offered large bribes to government officials, medical industry associations and foundations, hospitals and doctors in order to expand the company's market in China and raise the price of its medicine.\(^{31}\) Other western news sources cited comparable allegations involving the Chinese operations of Novartis,\(^{32}\) Lilly\(^{33}\) and France's Sanofi.\(^{34}\) Accusations related to corruption at various levels and in various forms, including offers of foreign travel and "sexual bribes". In the US media the possibility was raised that any American company found guilty of such practices in China might also be liable to prosecution under the US Foreign Corrupt Practices Act.\(^{35}\)

A firm may learn little in such matters from brushes with its critics and with the law. It is instructive to consider two snapshots of the behaviour of a single firm, some 20 years apart. In 1984 John Braithwaite concluded that 19 of the 20 largest US pharmaceutical companies had paid commercially significant bribes, particularly in developing countries, but not only in developing countries, to secure marketing approval for drugs and other objectives. This led him to conclude that there were few, if any, industries with an international corruption record comparable to the pharmaceutical industry in the 1970s. One of those 19 companies was Schering-Plough Inc.:

Schering-Plough reported questionable payments of $1.1 million between 1971 and 1976. Early disclosures of $0.8 million had to be supplemented in 1977 with further revelations. These included explicit reference to payments to secure product registrations.

In another foreign country, payments of approximately $220,000 were made during the years 1972 through 1976 to private consultants engaged to procure product registrations, or renewals thereof, in that country. In addition, in that

\(^{31}\) Hennigan M (2013), 'Big pharma firms subject of fraud inquiries in US, China and Japan', *Finfacts*, 16 July.


\(^{33}\) Roland D (2013), 'China pharma scandal widens as Eli Lilly accused of bribery', *Telegraph* (London), 22 August.


\(^{35}\) Kelton E (2013), 'Is big pharma addicted to fraud?', *Forbes*, 20 July.
same country, payments totalling approximately $17,000 were made in the
years 1972, 1975 and 1976 to consultants engaged to settle proposed income
tax assessments. Senior management has been advised that all or a portion
of the aforesaid payments may have been passed on to public officials responsi-
ble for processing the registrations or tax assessments although it has no
direct knowledge of any such payments.

In another country, payments in the amount of approximately $37,000 were
made during the years 1972 through 1976, in connection with applications for
product registrations in that country, to individuals who were part-time
consultants to a government agency responsible for issuing such registra-
tions.36

Taking due account of the effects of inflation over three decades, one can
then go on to cite – again verbatim – a report relating to the same
corporation as it appeared in a public interest newsletter in 2004, this
time relating to events in the United States:

Criminal Prosecution of Schering Sales Corporation: In 2004, Schering
Sales Corporation, a sales and marketing subsidiary of drug manufacturer
Schering-Plough Corporation, pleaded guilty and paid a $52.5 million fine on
charges that it paid a health maintenance organization (HMO) a kickback to
induce the HMO to keep Schering’s drug, Claritin (loratidine), on its
formulary (a list of drugs that the HMO covers for its beneficiaries). Schering-Plough also settled its False Claims Act liability and paid the United
States, 50 state Medicaid programs, and certain Public Health Service (PHS)
entities approximately $293 million for failing to report the company’s true
best price for Claritin to the Medicaid programs. At the same time, Schering-
Plough entered into a Corporate Integrity Agreement (CIA) with the
HHS/OIG37 to correct its government pricing and Medicaid rebate reporting
failures ...

Corruption in drug registration and approval may involve generic producers
as well as research-based manufacturers. In 1989, for example, the
United States FDA investigated a series of cases in which generic firms
had provided relatively small bribes to chemists and others in the agency
in order to secure either priority or a more favourable assessment of their
applications. Ironically, it was a pharmaceutical company, Mylan, that

36 Braithwaite J (1984), Corporate Crime in the Pharmaceutical Industry,
London, Boston and Henley: Routledge & Kegan Paul, p. 34.
General in the US Government.
38 Pharmwatch (2005), ‘Criminal prosecutions of Schering-Plough Corpora-
January 2010).
exposed a degree of corruption involving even the US drug approval process. Suspecting that some form of improper influence lay behind the fact that certain pharmaceutical products were approved for sale much more rapidly than others, Mylan hired private detectives who "caught FDA agents red-handed taking bribes in exchange for expediting drug approval". An FDA chemist was convicted in 1990 of receiving illegal gratuities totalling $4,300 from two drug firms, and was sentenced to prison, a fine and community service. Other chemists and FDA employees received lesser sentences and a series of company executives pleaded guilty and were duly sentenced.

Bribery has also been a feature of some attempts to gain approval for veterinary products. In 1997–8, according to various sources, the Monsanto company offered sums of between $1 million and $2 million to Health Canada scientists in an unsuccessful attempt to secure registration of its genetically engineered bovine growth hormone, which was intended to increase milk secretion in cows.

On occasion, government officials in other countries have themselves been prosecuted for taking bribes from the industry and an increasing number of countries have passed legislation to counter such malpractice. The Chinese government has in the meantime enacted its own anti-corruption legislation; this, as well as introducing an online procurement system, may counter bribery to some extent.

In some countries corruption in the health sector has become so widespread that no level of government is considered above suspicion; in the Philippines in July 2009 a senator publicly accused a major US manufacturer of seeking to bribe the country's president in order to

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39 Ausubel K (2001), 'When healing becomes a crime', Tikkun Magazine, 12 June.
41 Valentine PW (1989), 'Former FDA chemist gets 1 year in generic drug bribery case', Washington Post, 4 October.
43 Baxter J (1998), 'Monsanto accused of attempt to bribe health Canada for rBGH (Posalic®) approval', The Ottawa Citizen, 23 October.
secure changes in the proposed "Cheaper Medicines Law". One must bear in mind, however, that in politics and at the higher levels of government there is always a procedure for ongoing consultation at all levels of society, including business, and it is obvious that such consultation can sometimes lead to unjustified allegations that improper influence is being exerted.

5.2.4 Corruption of Trade

Sometimes a bona fide pharmaceutical company may be the victim of corruption exercised by others, especially counterfeiters. Wrage has provided an account of how a US company trading in a West African country found itself facing competition from an illegal group that was counterfeiting its products and securing its position on the market by payment to local officials. When the counterfeit products proved injurious to health, the US firm was charged with the damage caused by products that they had neither produced nor sold.

5.2.5 Health Services and Funding Agencies

Particularly where a new drug is not clearly superior, in terms of efficacy or safety, to those marketed earlier, the temptation to use particular forms of pressure to secure its adoption by health services and funding agencies can prove irresistible in commercial circles. That situation seems for example to have arisen with some newer treatments for schizophrenia. Consider Risperdal® (risperidone), developed by the Janssen-Cilag division of Johnson & Johnson, which belongs to the so-called "second generation" of antipsychotic drugs, all of which are claimed to be somewhat more acceptable than the first-generation compounds in this class, though as noted in Chapter 4 this claim is doubtful. In a case reported in 2008, corruption seems to have gone hand in hand with false advertising, manipulation and suppression of data. In a fraud lawsuit against Janssen and its associated companies filed in 2006 and amended in December 2008, the State of Texas raised allegations that Janssen had

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46 Ubac ML (2009), 'Pfizer "bribe" case brought before US gov't', Philippine Daily Inquirer, 21 July.
paid kickbacks to Texas health officials, distributed false marketing materials and deployed phony advocacy groups to get its Risperdal antipsychotic prescribed to low-income Texans. Despite the narrowness of the approval granted by the FDA and an early warning by the Agency against claiming superiority for the product, the defendant had according to the filing "developed and executed a marketing plan based on misrepresentation and concealment of material facts", notably when applying for a contract, benefit or payment under the Medicaid programme. The filing further alleged specifically that defendants had "provided inducements to the Texas state mental health decision makers, including honoraria".

As noted earlier (pp. 187–8) the Russian firm Protek was charged in 2007 with bribery of a national health insurance fund.

In essence, then, the companies involved in the above cases were accused inter alia of bribing state decision makers and of thus engaging in a "conspiracy" to breach the fiduciary duty that the latter owed to the community. Whatever the outcome of such proceedings, the charges are not dissimilar to those that have been levied elsewhere and against other pharmaceutical companies. The ultimate consequences of such acts, if proven, will be a distortion in the pattern of treatment of patients as well as financial loss to the health financing system.

The means employed to defraud health funding agencies vary, but the sums involved can be substantial. In 2004 the Attorney General of New Jersey announced that the state's Medicaid programme was to receive more than $2.1 million as a result of a national settlement which required GlaxoSmithKline to pay $87 million in damages and penalties to federal and state Medicaid programmes. As the Attorney General commented: "Every dollar lost to fraud or abuse is one less dollar available to help the most needy citizens of our state".


50 Anon. (2007), 'Head of Russian pharmaceutical co. Protek charged with bribery', op. cit.

5.2.6 Bribery Abroad

Under the anti-bribery provisions of the US Foreign Corrupt Practices Act of 1977, it is a felony for US companies and individuals to give or promise anything of value to a foreign official (or to authorize such gifts) with the intent of inducing the official to assist in obtaining or retaining business. A separate provision requires that in these matters companies record all business transactions in a reasonably detailed manner and implement adequate accounting controls to safeguard against misconduct. As of August 2012 at least eight of the largest US pharmaceutical companies were reported to be under investigation or to have been charged under the Act. The chief of the Securities and Exchange Commission’s Foreign Enforcement Division noted in 2012, when commenting on a $60 million settlement with Pfizer under the Act, relating to corrupt practices in eight countries:

Pfizer subsidiaries in several countries had bribery so entwined in their sales culture that they offered points and bonus programs to improperly reward foreign officials who proved to be their best customers.

In 2008, the US Department of Justice imposed a $2 million criminal penalty on the AGA Medical Corporation relating to allegations of illegal payments made to officials in China. Members of the company’s staff were stated to have used distributors in China to make illegal advances to government-owned hospitals and physicians to influence the sale of products. It was also alleged that payments were made to the China State Intellectual Property Office to influence the approval of AGA patents.

As of November 2009, the US Department of Justice was warning pharmaceutical companies that these anti-bribery provisions could be applied to foreign transactions at any point on the supply chain from procurement officers and administrators through to managers of state hospitals and health professionals. The payments allegedly made in the

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54 BBC (2012), ‘Pfizer pays $60m to US government to settle charges’, BBC News, 7 August.
Chinese cases noted elsewhere in this chapter could therefore, if proven, constitute an offence under US law. In 2004 it was found that Schering-Plough’s subsidiary in Poland had paid $76,000 in bribes to influence the decisions of a Polish government official, thereby helping the company to obtain hospital and pharmaceutical business. Moreover, the bribe payments were not accurately recorded in the company’s books and records. The firm was ordered to pay a civil penalty of $500,000 and to take certain other corrective measures. Among other things it was to retain an independent consultant agreeable to the Securities and Exchange Commission to review the company’s internal controls, record-keeping, and financial reporting policies and procedures, and required to adopt the consultant’s procedural recommendations.\(^{57}\)

In certain instances, the US authorities have even been able to take action in alleged instances of bribery involving both foreign firms and foreign markets. In one such instance the acts of the Netherlands’ AKZO Nobel NV were considered to fall within US jurisdiction by virtue of the concern’s having American depositary receipts which were registered with the Securities and Exchange Commission. Proceedings were duly brought by the Commission in the District Court for the District of Columbia against AKZO Nobel under the Foreign Corrupt Practices Act. It was alleged that the concern’s pharmaceutical division (NV Organon) and its veterinary division (Intervet International BV) had, when selling products to the former regime in Iraq under the UN Oil-for-Food Programme, paid bribes to Iraqi officials in order to secure orders. Such payments were explicitly prohibited by the Programme and in the framework of US and international trade sanctions on Iraq. The costs involved in bribery were charged to the UN, but untruthfully designated as “after sales service fees”. AKZO Nobel had also failed to devise and maintain a system of internal accounting controls to detect and prevent such illicit payments.\(^{58}\)

Analogous prosecutions relating to these illicit deals in Iraq were also brought in Europe. Organon (by then a division of Schering-Plough) was among seven companies that in 2008 were fined a total of €1.3 million ($2.1 million) for the bribes paid to the Saddam Hussein regime. Organon received a fine of €380,602 from a Dutch court for its


Involvement; the court added that it also intended to recover the profits made as a result of the deals.\textsuperscript{59}

In a similar case in the US, again involving abuse of the Oil-for-Food Programme in Iraq, Denmark's Novo-Nordisk company was obliged to pay a total of some $18 million in fines, civil penalties and disgorgement of profits.\textsuperscript{60}

It may be noted that the provisions of the United States' Foreign Corrupt Practices Act regarding offences committed abroad have inspired somewhat similar measures in most developed economies. The United Kingdom's Bribery Act of 2010 specifies as offences inter alia the bribery of a foreign public official and failure by a commercial organization to prevent bribery. The term "commercial organization" is considered to include not only companies incorporated in the UK and UK-formed partnerships but also companies and partnerships, \textit{wherever incorporated or formed}, which carry on business or part of a business in the UK. The latter provisions would appear to give the legislation, like that enacted in the United States, considerable global reach.\textsuperscript{61}

5.3 COUNTERFEITING

5.3.1 The Essence of Counterfeiting

The counterfeiting of medicines is, as of 2013, a global problem of vast dimensions. While the sale of counterfeit products is undoubtedly most widespread in the developing world, it occurs in all markets. Because counterfeit products are disseminated globally, both through normal trade channels and by way of the internet, the problem can only be solved by coordinated international effort.

At the outset, a clear distinction needs to be made between those copies of recognized drugs which, while in some cases illegal and in breach of trademark and patent laws, essentially possess the properties of the original, and those products that are not only illegal but also false and misleading. The latter merely have a superficial resemblance to the genuine product but may be of no medicinal value and are sometimes

\textsuperscript{59} BMI (2008), 'Organon fined over oil-for-food bribes', \textit{Business Monitor International (Pharma and Health Care Insight)}, July.
\textsuperscript{60} Cassel RL (2009), 'Novo-Nordisk pays $18 million in penalties for Iraq bribery', FCPA Blog, 11 May.
\textsuperscript{61} Wessing, 'The Bribery Act 2010 – How will it impact the pharmaceutical industry?' op. cit.
positively dangerous. Both types of product are of concern to the bona fide industry, which makes efforts to track them down to their source and bring prosecutions. It is however the latter type of counterfeit product that represents a major danger to public health and will therefore be the central topic of this review. A so-called penicillin ampoule that contains only powdered sugar or starch may cost the life of a child with pneumonia. A batch of falsified artemisinin, sold for the cure of resistant malaria, may decimate the population of an African village. In either instance the fraudulent product is also likely to have been made under far from ideal conditions (see Chapter 2), meaning that it may well be polluted with toxic impurities or pathogenic microorganisms and thus not merely ineffective but positively dangerous to health.

Exact definitions in this field are of crucial importance, especially since the creditable activities of the research-based industry to eliminate counterfeits have sometimes been all too closely linked to its more controversial efforts to counter the trade in genuine generic drugs. It is therefore not surprising that demands coming from the originator industry for governments to take strong action to suppress counterfeiting are often greeted with scepticism by developing countries, by public health advocacy groups, and by groups representing the reputable generic industry. When in May 2008, the WHO-based International Medical Products Anti-Counterfeiting Taskforce (IMPACT), upon which the research-based industry exerted considerable influence, introduced into the World Health Assembly a resolution to update WHO’s definition of a counterfeit medicine, it made this very error. It found itself vigorously opposed by India, which regarded the measure as one that would impede the country’s export of generic products in good standing. 62 Unless the originator industry and the legitimate generic industry are able to ratchet down the level of their mutual hostility in the interest of protecting the public, cooperation on solving the problem of dangerous counterfeits will remain difficult to achieve.

The risks to health of selling worthless or dangerous counterfeit medicines are evident and are reflected in increasingly strenuous efforts to counter the practice, as well as in increasingly severe penalties for offenders. 63

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63 See, for example: UNODC (2013), Mexican Senate Increases Penalties for Medicine Counterfeiters, UN Office on Drugs and Crime, 18 March.
5.3.2 The Extent of Counterfeiting

Information as to the global scope of counterfeiting or the sources of counterfeit products is incomplete, but individual country studies give a sufficiently clear picture of the seriousness of the situation and the need for action. A countrywide survey in Cambodia in 1999 showed that 60 per cent of 133 drug vendors sampled were selling under the mefloquine label tablets that in fact contained the ineffective but much cheaper combination of sulphadoxine and pyrimethamine (obtained from stocks that had been earmarked for destruction), or fakes that contained no active substance at all.\(^{64}\) Paul Newton et al. found that in five countries of mainland South East Asia 38 per cent of tablets claiming to contain the antimalarial artesunate were fake and of no value.\(^{65}\) Reviewing six such studies in 2007, Moloney noted estimated regional rates of counterfeiting ranging from 38 per cent to 53 per cent.\(^{66}\) Murray in 2012 claimed to have access to the findings of an operation conducted by the World Customs Organization during which 110 containers of pharmaceuticals entering West Africa were examined: “84 were found to contain fake pharmaceuticals. 82 million doses of fake medicine were confiscated.”\(^{67}\)

In developing countries, counterfeit medicines sometimes enter the public and private health systems on a massive scale through machinations in international trading, such as where counterfeits are supplied from abroad even though a genuine product has been ordered and paid for in advance. Smuggling in many cases accounts for the presence of counterfeits in an otherwise reasonably well-regulated market.\(^{68}\) Even in developed countries, counterfeits can to some extent infiltrate established supply systems. In the US in May 2002, thousands of vials of Procrit\(^R\)


\(^{66}\) Moloney J (2007), ‘Literature review for the research thesis: analysis of factors contributing to community vulnerability to substandard antimalarials’, Oslo: Department of General Practice and Community Medicine, University of Oslo.


(epoetin alpha), treatment with which normally costs some $8,400 annually, labelled as each containing 40,000 units, were found to contain only 2,000 units, while some vials contained only tap water.69

A relatively new area of abuse is the sale of drugs from unfamiliar internet addresses, sometimes claiming to be pharmacies (see Chapter 3), which commonly offer to undercut the retail trade's prices and to supply items without prescription, but which are very prone to supply entirely worthless products. The risk of counterfeit drugs being supplied when an order is placed with an unknown internet site appears to be substantial.

The Medicines and Medical Devices Safety Authority in New Zealand is one of the agencies that has warned prescribers and the public of the risks involved in purchasing drugs through offshore internet sites because of the considerable likelihood that they will be counterfeits.70 The Authority however also maintains a list of authorized pharmacies that can validly accept orders on the internet and may be expected to supply genuine products. Similarly, in the United States, the National Association of Boards of Pharmacy maintains a public register of authorized internet sources for drug purchases, and the FDA has explicitly warned against internet purchases from others, listing by name a large number of sites that have been shown to supply counterfeits.71

Large-scale counterfeit production is most likely to be found in countries with a considerable capacity for pharmaceutical manufacturing coupled with an insufficiently effective system of control and inspection. Many such products have been traced back to South East Asia, a considerable number originating in China, India and Pakistan. If the label indicates a country of origin at all, the information may be false. The regulatory system in India, split between federal and state authorities, is known to inspect only a tiny fraction of the manufacturing facilities in the country.72 Products from Asia have been found to move through the Central Asian Republics to the Middle East and onwards into Africa, and they are found on sale in all these areas.

70 NZMMDSA (2005), 'Counterfeit medicines – don’t fake concern', statement by the New Zealand Medicines and Medical Devices Regulatory Authority, Prescriber Update, 26(1), 15–16.
71 FDA (2008), Buying Medicines and Medical Products Online, Rockville, MD: Food and Drugs Administration.
Sometimes a bona fide pharmaceutical company may be the victim of corruption exercised by others, especially counterfeiters. As noted earlier (page 197) Wrage has reported such a case from West Africa where a bona fide company was charged with causing damage that was in fact due to illegal counterfeits of its products.\textsuperscript{73}

5.3.3 Detecting Counterfeits

With the sophisticated methods of pharmaceutical analysis available at the present day, such as the so-called DART method (direct analysis in real time),\textsuperscript{74} a counterfeit product can in a properly equipped laboratory be relatively easily distinguished from the original. The difficulty is that, in many parts of the world, the most advanced methods of analysis are either unavailable or in use only in central national laboratories. These laboratories are already heavily occupied with routine quality control and are unlikely to have sufficient capacity to undertake large-scale detection of fraudulent products. Most countries also maintain a network of less sophisticated laboratories handling local analyses. These are however more simply equipped and may be unable to detect increasingly sophisticated counterfeits.

The experience of the Republic of Laos is typical. Over a period of some 20 years, the nature of counterfeit products entering the country appears to have changed as a reaction to successive efforts to combat the trade. At first, the counterfeits were relatively crude imitations of recognized products. The printing and packaging were primitive, and with a little instruction the deceit could be detected by both a sales agent and a lay user. When the public became more alert to the practice, the presentation of the counterfeits improved, though the content was as valueless as ever. At this stage, some original manufacturers began to rely on the addition of a hologram to the packaging materials; fraudulent

\textsuperscript{73} Wrage, Bribery and Extortion: Undermining Business, Governments and Security, op. cit., p. 98.
manufacturers, however, produced a sufficiently close copy of the hologram to deceive consumers, and in due course they appear to have acquired sophisticated holographic equipment enabling them to copy original holograms precisely. In the meantime, there was a similar development towards greater sophistication as a means of reducing the likelihood that fraud would be detected. In the early 1990s, because of the appearance of false copies of the anti-malaria drug artusenate in which the active substance was completely absent, the Laotian authorities equipped their regional laboratories with simple equipment capable of determining whether artusenate was present in a given product. Shortly afterwards, the counterfeit producers began to include miniscule amounts of artusenate in their materials, quite insufficient to have any medicinal effect, but adequate to provide deceptively positive readings on all but the most sophisticated equipment.\(^7^5\)

5.3.4 Principles of Policy and Law

A paper by Paul Newton et al. published in the *British Medical Journal* in 2002 appeared under the title "Murder by fake drugs". The authors drew attention not only to the morbidity and mortality resulting from the trade in effective counterfeits, but also to the fact that certain of these products actually contained harmful ingredients.\(^7^6\) While the term "murder" was used here in a rhetorical rather than a legal sense, there is no doubt that this trade leads directly to loss of life and in many counterfeit cases, if there were the political will, homicide would be an apt charge. In a later paper from the Newton group, using the term "manslaughter" rather than "murder", individual case material was presented.

In February 2005, a 23-year-old man presented with fever to a rural hospital in Burma and was diagnosed as suffering from uncomplicated falciparum malaria. He was treated with an adequate dose of oral artusenate, labelled as having been made by Guilin Pharmaceutical in Guangxi, People’s Republic of China. Since artusenate derivatives were introduced in the area, not one of 600 patients with parasitaemia studied prospectively had died. In this case, however, the patient became unconscious on the third day with aggravated parasitaemia and died despite intensive treatment. The artesunate used to treat the man was found to be counterfeit. It carried a falsified hologram, and the main ingredient was

\(^{7^5}\) Sengaloundeth S (2007), ‘Verbal information to Dr MNG Dukes’, Vientiane, Laos, August.

paracetamol (acetaminophen), with a small amount of artusenate added.\textsuperscript{77} Unsurprisingly, such papers led the editors of the \textit{Lancet} in 2003 to put the question: "Who will take responsibility for corporate killing?"\textsuperscript{78} Other work from the Newton group stresses the major risk to public health resulting from this trade.\textsuperscript{79}

It is possible that the approach seen in the United Kingdom's Corporate Manslaughter and Corporate Homicide Act of 2007\textsuperscript{80} would prove useful in other countries for cases of this kind. The judicial concepts of "reckless homicide" or "depraved heart murder" which feature in various systems of law might also be helpful in this regard.\textsuperscript{81,82,83} They have been applied in cases concerning any form of reckless behaviour which might reasonably be considered to endanger life, even where such an act is not directed against a known and specific individual; they would therefore seem entirely applicable to cases resulting from the marketing of a product known to be grossly defective.

As Newton and his colleagues have shown, it is possible to document individual cases where this is necessary in order to bring charges. Ultimately one might hope to see an international criminal court being endowed with the authority to handle cases relating to this trade, but this does not at present appear to be a realistic prospect. International procedures to bring criminal proceedings are sometimes feasible where gross political crimes are concerned, but there is still little real hope of international commercial crime being dealt with in an analogous manner.


\textsuperscript{78} Editorial (2003), 'Who will take responsibility for corporate killing?', \textit{Lancet}, 361, 1921.

\textsuperscript{79} Cockburn R, PN Newton, EK Agyarko, D Akunyili and NJ White (2005), 'The global threat of counterfeit drugs: why industry and governments must communicate the dangers', \textit{PLOS}, 14 March.

\textsuperscript{80} Corporate Manslaughter and Corporate Homicide Act (2007) (c 19).

\textsuperscript{81} Collins KM (2002), 'Negligent homicide/manslaughter (involuntary)', \textit{International Journal of Justice Studies}, accessible through office@euro-online.org.

\textsuperscript{82} Strobel LP (1980), \textit{Reckless Homicide? Ford's Pinto Trial}, South Bend, IN: And Books.

An extensive report on counterfeit drugs drawn up by the WHO in 1999,\textsuperscript{84} with guidelines for tackling the problem in the framework of drug policy, provided an encyclopaedic overview of what might be done at various levels and by all parties. A major conference on the subject was convened in Rome in 2006,\textsuperscript{85} and WHO subsequently established a task force (International Medical Products Anti-Counterfeiting Taskforce (IMPACT)). Despite these (and other) manifestations of concern, there is still little sign of a truly coordinated global effort commensurate with the extent of the problem. When the International Conference of Drug Regulatory Authorities in 2004 examined a WHO proposal to tackle the matter through international law, it literally concluded "that further discussions are needed before a global treaty is introduced to tackle the growing trade in counterfeit drugs",\textsuperscript{86} a response that is sadly typical of the hesitant approach to the issue to date. It is clear that action is needed at every point, from the source to the final destination of the counterfeit product. The counterfeit movement is fuelled primarily by a dishonest urge for enrichment, but it is facilitated at every level by ignorance, indifference or both. A policy intended to defeat the problem is only likely to be successful if the matter is comprehensively addressed with a web of controls (see Part III). At this point, one can do no more than present some examples of significant efforts in particular fields.

Elimination at source is one promising approach. In September 2007, Dr Zhong-Yuan Yang reported to the International Scientific Committee of the US Pharmacopoeia on an initiative developed in China where pharmaceutical inspectors had been equipped with 40 mobile laboratories capable of taking samples from pharmaceutical production units for immediate examination. The equipment would render possible the detection on site of counterfeit products, enabling measures to be taken without delay.\textsuperscript{87}

\textsuperscript{86} Gibson ML (2004), 'Drug regulatory study global treaty to tackle counterfeit drugs', Brit. Med. J., 328, 486.4.
\textsuperscript{87} USP (2007), Statement by Prof. Zhong-Yuan Yang, member, advisor to the Guangzhou Municipal Institute for Drug Control, China, at the meeting of the US Pharmacopoeia International Scientific Committee, Tampa, FLA, September.
Elimination from the trade and internet is another promising approach. In developed countries, drug control agencies and inspectorates have been active in detecting and suppressing infiltration of the pharmaceutical supply chain by counterfeits. An investigation undertaken in 2002 by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) resulted in the seizure of over £1.5 million of counterfeit drugs intended for illegal sale to the public. The effort followed a series of such seizures at UK airports by customs officials. The medicines, sourced by a group that had specialized in the counterfeiting business, were filtered for sale through licensed wholesalers to pharmacies in the UK, and through internet sites based both in the UK and abroad. In September 2007, the individuals responsible within Britain were prosecuted and sentenced.

From the standpoint of those interested in the protection of public health, the idea — and the reality — that well-organized groups are deliberately introducing dangerous products into the medicine supply chain is difficult to grasp. It illustrates the very worst aspects of human nature. Perhaps it is a certain level of incredulity among the policy community that accounts for the tepid response. Most regrettably, a history of "crying wolf" by the originator industry in the face of legitimate generic competition has not helped matters. Yet counterfeiting is a reality and one of the most serious problems that the medicine supply chain must address. The perpetrators are dangerous people, and serious law enforcement is needed to confront them, with force if necessary. An appeal to conscience alone does not appear to be an effective approach.

5.4 FRAUD

The more complex and comprehensive the rulebooks become, the more subtle the means devised to circumvent them. Many instances of proven fraud in the pharmaceutical sector relate to pricing influences and are considered in Chapter 6; scientific fraud, including dishonest or incomplete presentations to regulatory agencies, was discussed in Chapter 1. Various other forms of fraud are reviewed below.

Despite repeated prosecutions of companies large and small for contravention of existing rules, the industry repeatedly strays far from the strait and narrow path in these matters. In September 2012, Public Citizen reported that the total sum paid out by pharmaceutical companies in the first 28 weeks of the year in the form of penalties or compensation

88 Lewcock A (2007), 'Massive counterfeit drug ring cracked', In-Pharma Technologist, 18 September.
for fraudulent behaviour involving Medicaid amounted to $6.6 billion, more than twice the sum paid out for the whole of 2011. Since these figures are based primarily on data from federal and state cases in the United States, and relate only to a particular type of fraud, the world total must be substantially higher. 89

5.4.1 Fraud on Payment Schemes

There are a variety of schemes in operation that aim to defraud drug payment systems, such as national health services or health funds in Europe and Medicare or Medicaid in the United States. Such schemes have been touched on earlier in this volume and are further described in Chapter 6.

5.4.2 “Channel Stuffing”

In some instances a pharmaceutical firm may contrive to expand its revenue by breaking the accepted rules of supply and demand in commerce. The earnings management technique, known in the United States as “channel stuffing”, where a manufacturer sets out to bolster its turnover (and thereby its stock price) artificially, at least in the short term, by offloading more of its products than usual onto the distribution chain, is one such approach. Wholesalers and retailers may merely be inconvenienced and their business affairs deranged by it, but the practice can also constitute fraud in the eyes of the watchdogs of the stock market.

In June 2005, the Bristol-Myers Squibb Company (BMS) agreed with the US Department of Justice and the Securities and Exchange Commission to pay $300 million in restitution and undertake a series of corporate reforms as part of an agreement with the government to defer prosecution on a charge of conspiring to commit securities fraud following the company’s failure to disclose its “channel-stuffing” activities in 2000 and 2001. Federal officials alleged that throughout those years BMS had concealed from investors its practice of enticing wholesalers through use of financial incentives to buy and hold greater quantities of prescription drugs than was warranted by the demand for those products. By the end of 2001, BMS’s channel stuffing had resulted in nearly $2 billion in “excess inventory” at the wholesaler level. Restitution and reform alone were apparently not considered sufficient to make amends; at the same

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time federal officials filed an indictment on two counts against three former officers or directors of the company.\textsuperscript{90} Substantial settlement fees and penalties were subsequently imposed on the two senior company officers who had been primarily involved in the practice, and each was disqualified from holding office in any public company for a period of time.\textsuperscript{91}

5.4.3 Substandard Medicines

While the issues relating to generic drugs as a class on the one hand and blatantly useless counterfeit on the other receive a great deal of attention, the problem of drugs that are simply substandard is all too readily overlooked.\textsuperscript{92} In countries with an efficient system of drug approval and inspection, most firms that are capable of obtaining marketing approval for their products will as a rule be able and anxious to maintain quality standards. They are also kept on their toes by the periodic visits of inspectors, taking and examining samples both from the production line and in the field, though as we saw in Chapter 2 this inspection regime can fail from time to time. In much of the developing world these standards are by no means always attained. Smaller producers may well succeed in delivering samples of adequate quality to the regulatory body when seeking marketing approval, but thereafter they may struggle (or in the worst case fail) to maintain that standard on the production line. In a paper produced for the American Enterprise Institute, Roger Bate estimated in 2012 that whereas well under 1 per cent of the medicines present on the UK distribution chain were substandard, the figure in developing countries was likely to attain some 10 per cent; such a situation could in his view well result in some 100,000 deaths annually.\textsuperscript{93} Some such analyses are likely to be distorted by the inclusion of outright counterfeit products when surveys are performed, but others have confirmed over the years the immensity of the

\textsuperscript{90} SEC News Digest, 9 August 2004.

\textsuperscript{91} Silverman E (2012), ‘Former Bristol execs settle channel stuffing charge’, Pharmalot, 4 February.

\textsuperscript{92} The World Health Organization in its publications distinguishes substandard medicines from what it terms “spurious falsely-labelled falsified counterfeit (SFFC) medicines”.

\textsuperscript{93} Bate R (2012), ‘The deadly world of falsified and substandard medicine’, AEI website, 16 October.
problem of substandard production. \(^94\) In Nigeria in April 2012 analysis of samples of 13 drug combinations used in Malaria showed gross variation in the content of active substances, constituting a formidable obstacle to the country’s anti-malaria programme. \(^95\)

Inevitably, investigations in this field are likely to produce evidence relating both to substandard production on the one hand and frank counterfeiting on the other. An ongoing study by India’s Central Drugs Standard Control Organization found a rapidly increasing incidence of offences in both classes. Having tested 137,000 drug samples over a three-year period, it found 6,500 to be of substandard quality, while 345 were fake drugs. The government announced that stringent penalties had now been introduced for the manufacture of “spurious or adulterated drugs” and that sampling was being intensified. Attempts to obtain valid information from whistleblowers had however proved unsuccessful. \(^96\) This growing problem in India was considered to reflect the highly fragmented nature of the industry. \(^97\)

5.4.4 Malpractice, Fraud and Injury

It is obvious that most or all of the forms of malpractice delineated in this chapter may lead not merely to expense, loss and contravention of the law, but also to physical and even fatal harm on a considerable scale. That is most clearly so where a medicine is inherently dangerous or ineffective, but physical harm may equally result from the fact that a recognized and much needed remedy is, for no sufficient reason, placed financially or topographically out of reach of those who need it, or that it is inappropriately employed. Those responsible may sometimes not be aware of the ultimate consequences of their acts or omissions, and they may indeed hardly be inclined to care, particularly in view of the fact that, in a complex society, victims may be so remote from the failure that was the ultimate cause of their suffering. Not uncommonly, one also encounters a situation in which a series of different failings have


\(^{95}\) Editorial (2012), ‘Sub-standard anti-malarial drugs in Lagos’, *Punch* (Lagos), 11 April.

\(^{96}\) Rediff News (2013), ‘Surge in cases of fake drugs; whistleblower plan draws a blank’, Rediff News App, 11 February.

\(^{97}\) Rediff News (2013), ‘Substandard and fake drugs are rampant in India because of the highly fragmented industry’, Rediff News App, 14 June.
converged to kill, and it can be difficult or impossible to determine where the essential fault (or faults) lay, or even to demonstrate cause and effect.

In the pharmaceutical field, criminal liability for injury is most likely to be recognized, alongside civil liability, where the ultimate failure has involved a clear breach of law and duty. That will clearly be the situation where any of the three forms of grossly improper practice considered in this chapter – corruption, counterfeiting and fraud – are concerned. The same will apply where the fault has breached specific laws and regulations.

Alongside those situations in which there has knowingly been a disregard for the law, one is confronted by those cases in which there is evidence of negligence. In Chapter 2 it was noted that in the making of pharmaceuticals there was no room for error. One might add that with pharmaceuticals there is hardly room for negligence or for neglect of duty at any level. More than five centuries ago, English law drew a distinction between ordinary negligence that could constitute a civil offence, and the gross form of negligence that called for a criminal penalty. Where medicines are concerned, with only a delicate borderline distinguishing efficacy from harm, almost any form of negligence may lie beyond that border and result all too readily in injury to the individual or the community.

5.5 CONCLUSION

When John Braithwaite wrote Corporate Crime in the Pharmaceutical Industry more than three decades ago, all the kinds of corruption, counterfeiting and fraud documented in the present book for the past three decades had been documented with cases from the 1950s until the early 1980s. One thing that has changed is that the monetary scale of the worst of the more recent fraud and corruption documented here is much greater, even allowing for inflation. Another is that we have seen heads of drug regulatory authorities in major economies such as China, India and Italy (one of whom in the latter case was also Chair of the European Community’s Committee for Proprietary Medicinal Products) convicted of accepting bribes. Such convictions were not something that happened before the 1990s.

Evidence of really major fraud and bribery is also more prevalent in the United States than it was before 1990, even if we have not seen FDA

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98 Thomas Pygot’s reading in the Inner Temple (1510), Cambridge University Library Manuscripts, Ee. iii. 46, fo. 47v.
heads go to prison. We argue in Part III that the 1986 reforms to the False Claims Act is one reason for this. In earlier chapters as well as this one, we have seen that nearly all of the really major US criminal enforcement actions in the twenty-first century ride on the back of the False Claims Act. Other countries can learn from recent US experience with the False Claims Act and in Part III we build an analysis of how the right kind of hybrid between public and private law enforcement is one key to combating fraud and bribery. We also argue that it is a reform that can be adapted to developing country circumstances. The burgeoning death toll in developing countries from the counterfeiting business that we have discussed in this chapter is one reason for considering this reform. Counterfeiting is a form of fraud that has clearly become more devastating in its consequences in recent decades because it has been adopted by major corporations, has been introduced into the internet marketing of dangerous and useless drugs and because its perpetrators have learnt how to corrupt state regulators. Counterfeiting is devastatingly worse because it is no longer largely a matter of minor, unsophisticated manufacturers. A worry about the future is that some of the more disturbing kinds of crime discussed in this chapter are particularly prevalent in the rapidly expanding second largest economy in the world, China. This is part of the imperative for the new drug diplomacy we discuss in Chapter 10.

We have seen in this chapter, however, evidence of significant bribery of FDA middle managers on the public record as when Mylan hired private detectives who “caught FDA agents red-handed taking bribes in exchange for expediting drug approval”, resulting in the conviction of four FDA employees. See Feuer E, Innocent Casualties: The FDA’s War Against Humanity, Pittsburgh, PA: Dorrance Publishing Company, p. 83; Valentine PW (1989), ‘FDA ex-supervisor facing charges in drug bribery; New York pharmaceutical firm implicated’, Washington Post, 10 May.
6. Pricing, monopolies, abuses and the law

6.1 FREEDOM AND PRICING

6.1.1 The Notion of Honest Pricing

Competition is the rallying cry of the free market. In the world of business, the stimulus that vigorous competition provides to develop ever better products and services, and to make them available at affordable prices, is at the heart of the commercial creed, a creed that is proclaimed with as much conviction in the pharmaceutical sector as in any other. In many sectors, there seems no reason to question the approach; in much of the western world it has supplied the bulk of the population with affordable clothes, with radios and reading matter, with opportunities for recreation and for travel, and with a fair market choice.

All the same, there can be a case for regulation where an entirely free market fails to meet some of society’s most essential needs, and particularly where, for one reason or another, the prevailing prices are such as to put an unreasonable burden on society or render medicines out of reach of the poor.

6.1.2 The Costs of Innovation

If the cost of developing and/or producing a particular life-saving medicine is indeed so high that it will be financially beyond the reach of some of the patients who need it, that fact may simply have to be accepted; in that case, public finance will have to be mobilized to solve the access problem and save lives. On many occasions, the industry has specifically and with much emphasis claimed that the costs of innovation are the principal reason for the high price of medicines.\(^1\)\(^2\) This chapter

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will argue, however, that there may be reason to question the grounds for setting particular levels of pricing, and that research and development (R&D) are not necessarily major factors. The 1999 data from the US Securities and Exchange Commission, already briefly referred to in Chapter 3, point to the fact that expenditure on promotion much exceeds that on research. The Commission’s findings, as summarized by Richard Laing, are presented in Table 6.1.

Table 6.1 1999 Pharmaceutical company data on R&D for the ten largest US pharmaceutical companies

<table>
<thead>
<tr>
<th>Revenue (billions) US$</th>
<th>Cost of goods (% of revenue)</th>
<th>Marketing and administration (% of revenue)</th>
<th>R&amp;D (% of revenue)</th>
<th>Profits (% of revenue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>17,557</td>
<td>28</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>Maximum</td>
<td>32,714</td>
<td>54</td>
<td>46</td>
<td>20</td>
</tr>
<tr>
<td>Minimum</td>
<td>10,003</td>
<td>18</td>
<td>16</td>
<td>6</td>
</tr>
</tbody>
</table>

The discrepancy between R&D costs and earnings may indeed be even greater than such studies suggest: the costs of “promotional studies” – superficial “try-outs” conducted to secure publicity rather than to serve any serious scientific purpose – tend for example to be classified in company records as “research and development” in order to obtain tax concessions, whereas they are in fact purely marketing expenses.

What is clear is that industry-sponsored statements on research and development expenses can be highly misleading. Merrill Goozner is only one of many commentators who have questioned the pricing of medicines, in his case in the United States. In his book The $800 Million Pill he examined among other matters statements made on behalf of the pharmaceutical industry, just after the turn of the century, that creating any one of a series of vital drugs and developing it to market would involve vast expenditure. The $800 million figure was derived from a publication by the Tufts University Centre for the Study of Drug


Development in November 2001, according to which the average new drug now cost $802 million in terms of research and development.\(^5\) The Center published a similar estimate of R&D costs in 2003,\(^6\) while in 2006 it increased the figure by a further 64 per cent to $1.32 billion.\(^7\) By late 2013, estimates of up to $1.8 billion were being discussed in the media.\(^8\)

It is relevant to note that the Tufts Center was originally founded in the 1970s at the University of Rochester, New York, with funding primarily from the Eli Lilly Company and headed by the late Lou Lasagna; its purpose was primarily to provide evidence that the industry could put before the US authorities to defend levels of drug pricing. While housed at Tufts University and having the appearance of an independent academic venture, the Center continues to be largely industry funded.\(^9\)

Although, as independent studies have shown, the costs of developing a new medicine are extraordinarily variable (rendering “average” figures problematic), and also difficult to calculate with any accuracy in the face of incomplete data,\(^10\) the Tufts Center estimate of development costs has been very firmly dismissed by critics.\(^11\) Light and Warburton, as independent academic researchers, have identified basic faults and misleading methodology in the Tufts papers; they consider the true costs of R&D for an average drug to be uncertain and highly variable but provide evidence that they may amount to some $58.7 million for a self-originated drug and some $43.4 million for a drug originating elsewhere.

\(^{5}\) Ibid.  
\(^{8}\) Österath B (2013), ‘From the lab to the medicine cabinet. The long road of drug development’, Deutsche Welle, 19 September.  
\(^{11}\) Noah, ‘The make-believe billion’, op. cit.  
(e.g. in an academic institution). These figures are only a small fraction of those advanced by Tufts.

In cases where a fundamental innovation of great medical importance proves to have been achieved in whole or in part by a public health institute or university, a pharmaceutical company securing the rights to the invention may earn entirely disproportionate profits. A case relating to the AIDS remedy AZT and involving various forms of improper dealing (including fraud on federal and state Medicaid programmes) was brought successfully against GlaxoSmithKline in the United States in 2004. According to a spokesman for the AIDS Healthcare Foundation (AHF):

They lied to the patent office in the 1980’s about discovering AZT’s ability to treat AIDS, and in doing so secured exclusive rights to manufacture it ... AZT was developed with federal assistance in the 1960’s, and the National Institutes of Health tested it for HIV use in the 1980s, but Glaxo secured patents on the substance in the 80’s and locked competitors out. They then priced AZT at thirty-two times the cost of manufacture, a practice repeated with every new AIDS drug since then.

We will also see this problem with the TaxolR case cited in Section 6.1.4 below.

6.1.3 Profits and Commercial Expenses

Alongside the costs of R&D and actual production, a firm will incur the costs of introducing a new medicine to the market, including the expenses involved in securing official approval, the much more substantial costs of promoting it to an appropriate audience in order to create demand, a contribution to company overheads, and the sums involved in rewarding shareholders. Once one has obtained reasonably reliable, or at least indicative, evidence of industry’s real costs in all these areas, one can proceed to consider whether the prices that it charges the citizen or the public purse are honest and justifiable.

In Chapter 3 evidence has already been advanced that the level of advertising and promotion maintained by the pharmaceutical industry is

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strikingly high. The figures in Table 6.1 and the extensive evidence advanced by Marcia Angell, Goozner and others point to the fact that it is not only extensive but also excessive. As Angell puts it, truly good new drugs sell themselves; much promotional expenditure is simply incurred to produce turnover for “me-too” drugs.\textsuperscript{15}

As to profits, to quote Marcia Angell:

\ldots year after year, for over two decades, this industry has been far and away the most profitable in the United States. In 2003, for the first time, the industry lost its first-place position, coming in third behind “mining, crude-oil production” and “commercial banks.”\textsuperscript{16}

In the decade since then, the pharmaceutical industry as a whole has fallen further behind other sectors of business as regards its profitability, but a number of large pharmaceutical corporations retain their elevated place on the Fortune 500 listing of successful businesses. A stock analysis from the New York Stock Exchange indicated that, as of 31 December 2011, Pfizer recorded a gross profit margin\textsuperscript{17} of 77.63 per cent, GlaxoSmithKline one of 73.23 per cent and Novartis of 68.97 per cent.\textsuperscript{18} Year by year, there are fluctuations in such figures, but those made public do not suggest the picture of an industry in crisis.

### 6.1.4 Pricing in the West

Although overpricing as a barrier to drug access has been most widely discussed as a problem affecting the developing world, figures such as those cited above clearly raise questions about the price of medicines in the United States. The exceptionally high cost of drugs in America has created serious problems both for insurance bodies and for underprivileged groups such as the retired elderly. What the American Association of Retired Persons (AARP) has described as “the skyrocketing cost of speciality drugs”\textsuperscript{19} has led both individuals and organizations to purchase drugs in Canada where government controls still keep the prices

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\textsuperscript{15} Angell, \textit{The Truth About Drug Companies}, op. cit., p. 133.

\textsuperscript{16} Ibid., p. xv.

\textsuperscript{17} In investment terms, gross profit margin is a financial metric used to assess a firm’s financial health by revealing the proportion of money left over from revenues after accounting for the cost of goods sold.

\textsuperscript{18} Source: http://www.stock-analysis-on.net/NYSE/Company/Novartis-AG/Ratios/Profitability (accessed 16 November 2012).

\textsuperscript{19} AARP (2008), \textit{AARP Watchdog}, 25 September.
substantially lower (see Chapter 4). For the elderly, bus tours to Canada to get prescriptions filled have become popular. 

Retail prices in Europe are generally rather lower and subject to various forms of control, but still need to be justified in terms of industry’s costs and the level of expenditure that can be considered fair and reasonable. In practice, the producer of a new drug is most likely to seek to market it at the highest price the market will bear. The demand for medicines is growing; the belief that a new medicine will be superior to what has gone before will create a willingness to pay the higher price that is likely to be demanded. That willingness is likely to be further enhanced by demand creation and seductive advertising. Given such a situation, the producer will set about calculating the maximum price that it can demand without risking negative feedback from the customer. This is likely to be the price which well-heeled consumers may be prepared to accept, and which they are likely to pay at the pharmacy without protesting. There may be a degree of resistance from public health providers and insurers, but they can be quietly provided with modest discounts for volume purchases. Many other individuals, even in the upper middle classes, may find that when they have a pressing need for a life-saving drug it is beyond their means. As of October 2012 a worldwide meeting of cancer specialists in Lugano, Switzerland, noted that the latest anti-cancer drugs were now priced at such a level that treatment with them was becoming unaffordable, even in rich countries, and the prices charged were being seriously questioned. The history of the cancer chemotherapy agent Taxol® (paclitaxel), which came to prominence more than two decades ago, is particularly striking. 

In 1967, Wall and Wani in the United States, working in a publicly funded programme at the National Cancer Institute (associated with the National Institutes of Health), isolated a mitotic inhibitor (paclitaxel) from the bark of the Pacific Yew tree, Taxus brevifolia. Realizing its

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possible potential for cancer treatment, the Institute conducted animal studies followed by phase I and some phase II studies in humans. By 1988 remarkable efficacy had been demonstrated, notably in cancer of the ovary, in which it was much superior to other drugs. It was however calculated that to provide sufficient material to treat all cases eligible for paclitaxel treatment in the United States alone would require the destruction of some 360,000 trees annually, raising environmental and supply concerns. Contact was therefore sought with a pharmaceutical company and in due course an agreement was reached with Bristol-Myers (later known as Bristol-Myers Squibb or BMS), which essentially acquired rights to the discovery of paclitaxel and would finance studies to solve the supply problem as well as expanding clinical testing. The firm subsequently identified other sources and obtained marketing approval for the drug in the United States and elsewhere. The market price was exceptionally high; during a Congressional debate it was stated that the company was charging 20 times what it was paying for the raw product; worldwide, the price proved problematic and even prohibitive for health-care services. BMS argued before a Congressional panel in 1993 that the exceptional price was justified by an investment of nearly $1 billion in research. In the meantime, BMS was using lobbying and litigation in other countries to obstruct the marketing of low-cost versions of paclitaxel (see Section 6.3 below).

The claim that BMS had invested nearly $1 billion in paclitaxel has been dismissed by critics, in the light of available figures, as grossly exaggerated. In 2003 the United States General Accounting Office calculated that the National Institutes of Health had invested in all $484 million of public money in the relevant research programme up to 2002. BMS, which up to 2002 had earned over $9 billion from Taxol® sales, had paid only $35 million in royalties to NIH. This experience resonates with that of the AZT case cited in Section 6.1.2 above.

23 In typical markets the price in 1999 was set at some $700 for a 100 mg vial. Infusions of 175 mg/m² were advised which for an average patient would equal some $1225 on each occasion, with three weeks between courses. A year’s treatment might therefore cost some $20,000. (See Felleskatalog (1999), ‘Felleskatalogen: medisin’, Oslo.)


There is no doubt that, as a result of the involvement of a pharma­ceutical company, paclitaxel reached the markets earlier than would have been possible had its development been handled only by a public sector that lacks investment capital. It was also the achievement of a pharma­ceutical firm to identify other natural and semi-synthetic sources for the starting material. Sadly, however, the story at the same time shows the lengths to which such a company may go, when the opportunity permits, to allow its own financial interests to weigh more heavily than those of seriously ill patients, public sector research, and the public purse.

In some situations companies working in western economies have taken advantage of the pricing rules set by public health funding agencies in order to enrich themselves improperly at the expense of the public purse. The issue of fraud in such payment schemes was already touched on in Chapter 5 (Section 5.4.1). The Medicare and Medicaid systems in the United States have repeatedly found themselves deceived in various ways.

One technique that has been employed by some firms in the US is to charge the Medicaid system a high "standard" price for medicines, while offering discounted prices to private insurers. In June 2008, an Alabama state court jury found GlaxoSmithKline and Novartis guilty of defrauding the state Medicaid programme in this way; GSK was ordered to pay the state $80.8 million, Novartis about $33.7 million, in compensatory damages. State attorneys had also sought punitive damages, but these were refused by the jury. Both firms were reported to be considering an appeal.26

As noted earlier, the reaction to this type of abuse has been the passage in the US of the "Best Price" Statute (see Section 5.2.2).27

Another trick has involved double billing. In 2005 GlaxoSmithKline paid over $150 million to resolve a prosecutor's charges that the company had violated the False Claims Act in the marketing of two anti-emetic drugs. In the case of one of these drugs, according to the prosecution, GSK had engaged in a "double dipping" billing scheme; health professionals were encouraged to save unused vials from packages of KytrilR (granisetron) that had already been charged to a health programme. The unused vials were then put together to form a new unit that could be used for another patient and then billed once more to

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Medicare or other federal health care programmes. Commenting on the case, the Inspector General of Health and Human Services remarked that "any pharmaceutical company that intentionally inflates the cost of prescription drugs with elaborate pricing schemes robs states and beneficiaries nationwide of millions of Medicare and Medicaid dollars".

6.1.5 Pricing in the Developing World

In January 2009, the *Lancet* published a study, with the best credentials imaginable, of the price, availability and affordability of just 15 essential medicines in a large series of low- and middle-income countries. The findings were little short of alarming, profiling now more starkly in hard figures some of the problems that the UN Millennium Project had defined in a 2005 report. In the public sector, according to the *Lancet*’s findings, the average availability of these essential medicines in low-cost generic form through the various public supply systems was appallingly low: 54.4 per cent at best and in some instances less than 30 per cent. The prices at which these governmental systems were procuring drugs were only a little more than recommended reference prices, but low procurement prices did not always translate into low prices to the patient. In the private sector, patients were found to be paying 9–25 times the international reference prices for the lowest-priced generic products and over 20 times the reference prices for branded products. Drug treatment for acute and chronic illness was in many countries unaffordable for those who needed it. Some of the pricing problems arose at the import level, but mark-ups at the wholesale and retail levels made the problem a great deal more severe, while in some countries taxes of up to 15 per cent were levied. As one of the authors of the *Lancet* study commented to the media: "This leads people to buy partial treatment courses for communicable diseases like malaria; interrupt what should be continuous

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treatment for chronic diseases like diabetes; spiral into debt; or, more likely, go without treatment".31

The policies of the research-based drug manufacturers in this situation have varied greatly. There are those which, over the years, have continued to drive a hard bargain – or refused to bargain at all, content to thrive on their existing prices while loudly trumpeting the shortcomings and unreliability of generic suppliers. Others have indeed made a positive effort to accommodate the needs of the public sector agencies and missions in the developing world by adjusting their prices down to a more modest, though sometimes still only marginally acceptable, level. Local managers of such firms who did attempt a flexible approach sometimes found themselves in hot water in their home environment. As one company representative recalled in later years:

As the firm’s representative in Kenya, Uganda and Tanzania I was authorized by Head Office to strike whatever bargains might be called for, within certain limits, when it came to selling to the National Medical Stores or the church people. Sometimes we ended up with prices not all that much higher than the Indians were charging for their generics, and the procurement people were often willing to pay the difference because they knew that we were supplying quality, and with the Indians they couldn’t ever be sure. Management stuck up for what we were doing, even when they got a tough letter from the Federation accusing them of breaking ranks. The local trade were pretty furious too, because they were still having to buy and sell the same items at premium prices – no bargaining allowed there. What finally put paid to the whole thing in our case was when some of the stuff we had almost been giving away leaked into the black market and was shipped back to Europe to be sold for a good price there with the profit going to the smugglers. At that point we had to go back to hard bargaining.32

The problem of illegal reimportation of preferentially priced medicines from developing countries into western markets – delivering ill-earned rewards for smuggling – is one to which the pharmaceutical industry has rightly objected and for which no complete answer has been found. It remains a major disincentive to flexible pricing for poor populations. Unfortunately, too, the possibility of such leakage across frontiers and oceans provides those firms that still prefer to strike a hard bargain with the developing world with an all too ready excuse to do so. The policy of maintaining prices at the highest level that the market will bear is one

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that was developed in relatively affluent western societies and that no doubt has its place when one is selling non-essential products in a competitive situation, but it is fatally easy for it to become a universal leitmotif.

Roy Vagelos, a former CEO of Merck, has described very well in his book *Medicine, Science and Merck* the pressures that he experienced within his company to raise prices, for no other reason than that it was possible to do so.33

When such principles are applied heartlessly to the developing world it is hard to set aside the view that their application constitutes a dangerous and inhumane habit. Precisely at the time that Vagelos, now retired, committed his thoughts to print, his successors at Merck found themselves engaged in precisely the sort of ethical dispute that he had feared.

In 2004 Merck was strongly criticized by the idealistic physicians’ association Médecins Sans Frontières (MSF: Doctors without Borders) for what was alleged to be its failure to carry through in countries hardest hit by HIV/AIDS a promised price reduction on its first-line antiretroviral drug efavirenz. In October 2002, Merck had announced that in countries in which adult HIV prevalence was at least 1 per cent and in those designated as “least developed” it would introduce a new once-daily 600 mg tablet formulation of efavirenz priced at $0.95 – 30 per cent less than the price of three 200 mg capsules. According to MSF, Merck subsequently broke its promise to make its new formulation available in these countries, largely having failed to ensure that it was registered there. Denying the accusations, Merck pointed out that, through no fault of its own, registration was taking time in some of the countries concerned, but that in certain of them special arrangements had been made to provide access before full approval. It added that the prices of three 200 mg capsules and one 600 mg tablet of efavirenz were not equivalent because they were two different products, involving different manufacturing processes. A spokesman for the Global AIDS Alliance considered Merck’s actions to be symptomatic of “tragic complacency” and to be “very disappointing and irresponsible”; originator companies would have to do much more than they were now doing to reduce prices, implement outlicensing, transfer production technologies, and to ensure

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access to bulk products. A spokesperson for WHO stressed the need for Merck to keep its promises.\(^{34}\)

Such disputes are not uncommon in the vexed world of drug pricing for the world’s poor. It is entirely true that regulatory delays can impede progress, but it is equally true that manufacturing costs – being as small a proportion of retail prices as they are – rarely constitute a valid reason for maintaining unreasonable price levels. That point was made in Chapter 3 but it deserves special emphasis in the developing country situation where a great many patients die because they cannot afford treatment. Even the drugs developed for the treatment of AIDS, which are commonly sold at extraordinary prices, can cost very little to make.

An investigative journalist for a leading US newspaper examined the prices and costs of AIDS drugs in 2001 when GlaxoSmithKline was selling its product Combivir\(^R\) (lamivudine with zidovudine) on the American market at a price amounting to about $7,000 per patient year. In fact the active ingredients of the drug could be bought for some $240 on the international generic market. Cipla of Bombay, India, was offering a generic version of Combivir at just $275 for a year’s treatment. According to the same report, Bristol-Myers Squibb was selling its AIDS drug Zerit\(^R\) (stavudine) in the US for some $3,400 a year, but planned to make it available in Africa for $55, which it claimed was below cost. However on the generic market the active ingredient was available for $23, and Cipla was prepared to offer the finished product for $40 a year.\(^{35}\) The figures change as the years go by (as of 2009, the price of branded Combivir in the United States had risen even further)\(^{36}\) but the phenomenon remains.

On occasion, the fact that a particular manufacturer has a monopoly on a much-needed medicine renders it possible to deprive the population of a developing country of a vital medicine in retaliation for governmental measures to which commercial management objects. Abbott produced a combination of lopinavir and ritonavir for the treatment of HIV/AIDS. It was a valuable drug for which there was a considerable need, though it had the disadvantage for a tropical country that it was poorly stable under


\(^{36}\) See price comparisons published by http://aids.about.com/od/hivmedicationfactsheets/a/drugcost.htm in April 2009, citing a price of $752.64 monthly, i.e. $9,031 per year.
warm conditions. For Thailand, Abbott set the price at a level corresponding to $2,967 per patient yearly, later reducing this under international pressure to $2,000 yearly, despite the fact that the average income in Thailand was only $1,600. The Thai government therefore issued a "government use" order as permitted under the TRIPS agreement (see Section 6.2.1 below), to enable it to buy a generic equivalent at a substantially lower price. In retaliation, Abbott withdrew all its new drug applications in Thailand, including one for a heat-stable version of the lopinavir/ritonavir combination that it was already selling in other countries\(^{37-39}\) (see also Chapter 4).

At the very least such an act would seem antisocial and a symptom of the utter contempt in which a company may hold both patients and governments (see Section 6.4.7 below).

### 6.1.6 Striving for a Balanced View

It is possible to estimate, on the basis of reasonably reliable data from various sources, the total amount spent yearly on medicines throughout the world. That amount, it seems, would, if wisely expended, be sufficient to supply the entire population with rather more than a range of essential medicines, as well as funding new drug development and basic information services, in addition providing a reasonable return on whatever capital has been invested in the sector. But it is not wisely expended. A great deal is wasted, notably in the purchase of worthless counterfeits, thereby merely enriching criminals – mostly corporate criminals rather than common ones. A great deal more is frivolously spent, either on wasteful promotion or on the sort of new product development that is unlikely to produce any added value. The upshot of all this is that a small proportion of the world’s people are adequately supplied, or over-supplied, with costly medicines, while the remainder of the population is grossly deprived of the products they need.

If in all these respects the situation were to be corrected, the medicines sector would be a happier one and the world’s population healthier.

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Better health would bring with it greater productivity and more wealth, as a result of which the situation could only continue to improve.

Very slowly, in bits and pieces, efforts are being made to help the world out of this unedifying predicament. Here and there, where idealism is given a chance, one can discern some progress, but it is painfully slow, and on occasion where the community has moved one step forwards, it has then moved two steps back. Perhaps the most crying need is for honesty: is that too much to demand? At least one should now take a look at the sort of malpractice and avarice that at every turn threatens to thwart progress.

6.2 PATENTS AND MONOPOLIES

6.2.1 Patents Then and Now

As noted at the start of this chapter, free competition is the watchword of the commercial world. And yet, in an apparent paradox, one encounters repeatedly in this same world, and most particularly where pharmaceuticals are concerned, a craving for the safe haven provided by monopoly rights, where business can be protected from the troublesome attentions of competitors.

The existence of legal monopoly points up the ambiguity felt by the executive about the impropriety of illegal monopoly. Indeed, pharmaceutical executives are socialised to perceive moral virtue in anticompetitive pricing practices.40

The primary mechanism by which monopoly can be secured for a given period is of course the grant of a patent. The history of patents is a lengthy one. In England, "letters patent" had been granted to inventors from the fourteenth century onwards, but the first detailed legislation on the subject was that introduced in the Republic of Venice by an edict dated 19 March 1474. To quote part of the edict's very lucid original text:

Any person in this city who makes any new and ingenious contrivance, not made heretofore in our dominion, shall, as soon as it is perfected so that it can be used and exercised, give notice of the same to our office of Provveditori de Comun [The State Judicial Office], it being forbidden up to 10 years for any

other person in any territory and place of ours to make a contrivance in the form and resemblance thereof, without the consent and license of the author.\textsuperscript{41}

Other states with an active commercial sector followed suit. The system served its purpose of protecting and encouraging the innovator. All the same, difficulties arose from time to time, characterized particularly by complaints that excessive monopolization was having a stifling effect on trade, competition and initiative. The English Parliament's Statute of Monopolies, passed in 1623 in the reign of King James I, was designed to correct the situation, replacing the original system by an entirely new one:

\begin{quote}
All Monopolies and all Commissions, Grants, Licences, Charters and Letters Patent heretofore made or granted or hereafter to be made or granted to any Person or Persons, Bodies Politick or Corporate whatsoever, of, or for the sole Buying, Selling, Making, Working or Using any Thing within this Realm ... or of any other Monopolies, or of Power, Liberty or Faculty ... are altogether contrary to the Laws of this Realm, and so are and shall be utterly void and of none effect and in no wise to be put into use or execution.\textsuperscript{42}
\end{quote}

Having thus disposed of the residues of an excessively monopolized past, the Statute went on to maintain and extend the right of the Crown to issue:

\begin{quote}
... Letters Patents and Grants of Privilege for the Term of one and Twenty Years, or under, heretofore made of the sole Working or Making of any Manner of new Manufacture within this Realm, to the first true Inventor or Inventors of such Manufactures which others at the time of the Making of such Letters Patents Grants did not use ...\textsuperscript{43}
\end{quote}

With increasing international trade in the centuries that followed, a need ultimately arose to introduce a greater degree of uniformity in the various national systems. That was in some measure achieved in 1883 when The Paris Convention for the Protection of Industrial Property was signed; the Convention remains in force and as of 2012 had been adhered to by 174 countries. Despite progress towards such virtually worldwide unanimity on some basic principles, the twentieth century brought new challenges to the system. For one thing, multinational corporations were emerging and pressing the view that a global company serving a global market


\textsuperscript{42} Statute of Monopolies, 1623 (21 Jac. 1, c.3).

\textsuperscript{43} Ibid.
needed a globally uniform patent regime, rather than a jigsaw of somewhat divergent national systems. A particular problem in the pharmaceutical sector was that a number of major countries did not grant or recognize patents on medicinal products, considering that in the public interest there should be a free market in the field of health.

A much more general challenge was the new diversity of the world, with the emergence of a large number of newly independent developing countries where purchasing power was weak. It was clear that the views of such countries on a patent system that would provide protection to the western producers of high-priced products might differ substantially from those of the industrialized west. As outlined in Chapter 4, the controversial debate that ensued, with heavy lobbying by various industrial sectors demanding greater protection, led to the implementation in 1995 of the TRIPS agreement and with it the introduction of a virtually watertight worldwide system of patents. It was clear that this could endanger the access by poor populations. It was therefore followed, to the consternation of much of western industry, by the compromises reached at the Fourth WTO Ministerial Conference held at Doha in 2001, which introduced what are now known as the "TRIPS flexibilities". The resulting Declaration established the right of governments to issue compulsory licences on drugs without the need for the patent holder to agree. In a country where drugs were prohibitively expensive, the government would now be entitled to import items from a location where prices were lower, again without seeking the permission of the patent holder. Countries at the lowest level of development would not be required to conform immediately to the TRIPS rules, at least until 2016. As Ellen 't Hoen has put it:

... the Doha Declaration ... signalled a sea change in thinking about patents and medicines, and is at the root of a cascade of activities aimed at reformulating Intellectual Property protection as a social policy tool for the benefit of society as a whole rather than as a mechanism to protect only limited commercial interests.45

44 These included France (until 1960), Switzerland (until 1977), Italy (until 1978), Sweden (until 1978) and Spain (until 1992), as well as many non-European countries. See Dutfield G (2009), Intellectual Property Rights and the Life Science Industries: Past, Present and Future, London: World Scientific Publishing.
Equally striking was that this sea change had been brought about largely thanks to the influence of social and consumer forces, and in spite of the might of the wealthy and well-organized industry.\textsuperscript{46}

As of 2013 doubt remains as to whether this compromise, still violently contested by the patent lobby, will in the long run prove sufficient to enable developing countries to provide their populations with affordable drugs in sufficient quantities and over a sufficiently long period of time. The industry response has been to persuade the United States and European Union to negotiate “TRIPS plus” bilateral trade agreements that have put the compromise greatly in doubt.

6.2.2 Patent Virtues and Vice

Over five centuries, patents have in many situations continued to serve their primary purpose of allowing inventors to profit from their inventions for a fair period. Under current patent legislation, in line with global policies laid down within the World Trade Organization, a patent will be valid for a period of 20 years from the time it is granted. During the first few years the product is likely to be still under development, and thereafter it will be subject to the regulatory process that, in the pharmaceutical sector, precedes marketing. Thereafter, however, and for the remainder of the 20-year period, the monopoly created by the patent will enable the pharmaceutical manufacturer to earn handsomely from its product, cosily protected from the effects of competition in the market. All this is precisely what the patent system was intended to do.

If there are certain doubts today regarding its proper place in the field of pharmaceuticals, those doubts do not relate to the desirability of ensuring that the innovator enjoys a reasonable reward, in this sector as in any other. Other objections however apply. First, there is some room for doubt regarding the belief that, in the pharmaceutical sector, the patent system does at the present day truly promote innovation.\textsuperscript{47} Data cited earlier in this volume point to a serious decline in pharmaceutical inventiveness during the closing decades of the twentieth century. Should the rate of innovation recover in the years still ahead, as it might still do, the question will be whether that is due to the role of patents or to fundamental changes in the approach to research, for example the rise in biotechnological as opposed to chemical innovation. An analysis by


Kesselheim and Avorn suggests, to quote them literally, that "drug-related patents that arise in non-profit settings are at least as likely to be important innovations as patents from the commercial sector". Beyond this, however, there are considerable misgivings about the misuse of the system; such concerns are not dissimilar to those expressed in England in 1623; they relate quite simply to the fact that the system has rendered possible the excessive use or frank misuse of monopoly positions.

The most apparent form of abuse concerns gross overpricing, putting a vital product out of reach of those who most need it. Beyond this, however, the holder of a patent may extend its influence in various ways and to an unreasonable degree, either by using it to form a cartel, by broadening its scope or by artificially extending its duration. Not all these practices are illegal, but each of them holds potential competitors at a greater distance than the mere possession of a basic patent might do. All these practices must be considered below.

There are yet other forms of abuse of the patent system, devised by originator companies primarily to exclude generic equivalents from entering the market when they have a right to do so; they have been reviewed by Jorge. Such malpractice is fortunately being brought to the attention of governments and of the courts, but it is as of 2014 still inadequately challenged.

In December 2012, the European Court of Justice in Luxembourg upheld a €52.5 million antitrust fine levied by the European Commission on AstraZeneca for blocking the entry to the market of a cheaper (generic) version of what was then its bestselling product, the ulcer drug Losec\textsuperscript{R} (omeprazole). "The abuses must be characterized as serious infringements, and consequently the amount of the fine cannot be reduced for those reasons", the Court declared. The case hinged on charges that the company gave misleading information on Losec\textsuperscript{R} to several national patent agencies during the period 1993–2000. This blocked not only the marketing of the cheaper generics but also the parallel importation of Losec\textsuperscript{R} itself from markets where lower prices prevailed.

\begin{itemize}
\item[49] Jorge MF (2010), 'Governments have begun to act but more needs to be done to stop patent lawsuit abuse', \textit{J. Generic Medicines}, 7, 215–16.
\item[50] Ibid.
\item[51] Chee FH and B Hirschler (2012), 'Top EU court upholds AstraZeneca fine over ulcer drug', \textit{Chicago Tribune} Business Section, 6 December.
\end{itemize}
One must note that this was not AstraZeneca's only approach to maintaining its highly profitable sales, as we will see in Section 6.2.6 below.

### 6.2.3 Pricing Policies

The holder of a patent can earn well from the monopoly granted to it. The actual sums expended in manufacturing a typical medicinal product are, after all, as a rule relatively small, particularly once mass production has got into its stride and the processes of synthesis and quality control have been streamlined. A major manufacturer will therefore have very considerable scope to set prices at whatever level the market will bear. The point at which straightforward commercial brilliance in this respect lays such a burden on the community that it becomes socially unacceptable is an issue to which we shall return in Section 6.5 below.

### 6.2.4 Cartels

A private cartel$^{52}$ is a formal agreement, often secretive, between two or more firms with similar interests in the market, under which they undertake to collaborate rather than compete. In the pharmaceutical field it typically concerns firms selling identical or closely similar products which are not generally available from other sources. The intention of such collusion is to increase profits by preventing the emergence of competition. The partners will agree on complementary or joint commercial approaches; these may include arrangements for price fixing, bid rigging or allocation of customers or territories. The formation of private cartels is generally forbidden under laws enacted to ensure fair competition, but they continue to erupt.

One of the most remarkable cases of price fixing by a cartel, involving several successive prosecutions, concerned the Swiss firm Hoffmann-La Roche and partner firms in France and Germany. In 1973, Stanley Adams, who had been the firm's world product manager in Basel, contacted the European Community, presenting evidence that Roche had been breaking antitrust laws, engaging with its competitors in price fixing and market sharing for vitamins. Roche was fined accordingly, but an administrative error in a Community office allowed the company to obtain some of the relevant documents and thereby to discover that it was Adams who had alerted the Community to the matter. He was arrested in

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$^{52}$ A "public" cartel is one in which a government participates; such a cartel cannot be ruled illegal.
Switzerland for unauthorized disclosure – an offence under Swiss law – and imprisoned. His wife, having received information suggesting that he might face decades in jail, committed suicide.\textsuperscript{53} In fact Adams was released after six months but arrested again more than once before eventually escaping to Britain, where he published an account of the events.\textsuperscript{54}

Despite the sentence, Roche maintained or regained its place in the price-fixing cartel for vitamins which also included BASF of Germany and Rhône-Poulenc of France. In 1999, with Roche holding some 40 per cent of the global vitamin market, the firm was again prosecuted, this time in the United States; the company pleaded guilty and paid a record $500 million fine. Dr Roland Brönnimann, a former executive of the firm, also pleaded guilty and was sentenced to five months in prison and a fine of $150,000 fine for his role in the conspiracy.\textsuperscript{55} The European Commission in the meantime brought renewed charges on the same score and in 2001 fined Roche a further €462 million. The European Commission’s competition director general commented that this was the most damaging case the Commission had ever investigated, as it had continued throughout the 1990s and involved substances vital for healthy living.\textsuperscript{56,57,58}

In 2003, Rhône-Poulenc Biochimie SA, a subsidiary of France’s Aventis SA, agreed to plead guilty and pay a $5 million fine for participating in a conspiracy to fix prices and allocate customers for a chemical used to slow the rate at which dyes disperse throughout the body during X-ray examination and other medical imaging procedures. In addition a St Louis, Missouri federal grand jury indicted Eric Descouraux, a former sales and marketing director in the firm, for his role in the conspiracy. According to papers presented to the court, employees of the firm had met annually in Europe over a nine-year period with representatives of a competitor to agree on the prices each would charge their customers worldwide. Additionally, the conspirators exchanged sales and customer information in order to monitor and enforce adherence to the

\textsuperscript{54} Adams S (1984), Roche Versus Adams, London: Jonathan Cape.
\textsuperscript{55} DoJ (1999), ‘Hoffman-La Roche executive pays fine, does jail time’, US Department of Justice, 19 August.
\textsuperscript{56} Anon., ‘Blowing the final whistle’, op. cit.
\textsuperscript{57} It may be noted that Roche sold its vitamin business in late 2002 to the Dutch chemical group DSM.
agreed prices and allocation of customers for pharmaceutical grade methyl glucamine sold in the United States and elsewhere.\textsuperscript{59}

6.2.5 The Broadening of Patents

Essentially, a patent is supposed to define in very exact terms the invention to which it affords protection. Where a pharmaceutical created in the laboratory is concerned, that will in many cases comprise a definition of the exact chemical structure of the active substance and the pharmacological properties that it has been shown to possess. It has however been said that “An avaricious inventor will seek protection not merely for the house that he has built, but also to prevent others from building in the garden, on the estate and if possible in the province and the nation around it”.\textsuperscript{60} Not surprisingly innovators, avaricious or otherwise, have commonly found themselves wrestling on this issue with conscientious patent officers (and more recently with protestors from civil society) who consider that an innovator is seeking to claim a broader monopoly than that to which it has a reasonable claim. In the first place the innovator will seek to phrase the definition of its product in such a manner that protection will extend more broadly, encompassing not only the particular molecule for which it was granted but also a range of possible variants on the structure. A budding competitor whose product is distinguished from the original by nothing more than the addition of a double bond or the substitution of an ethyl group by a phenyl group is likely to find the road to the market blocked by the basic patent. The innovator may also seek to define the scope of the patent so as to cover intermediates used in the course of synthesis or perhaps even the entire chemical technique used to create it in the laboratory. It is this issue, more than any other, that has led critics of the patent system to condemn it as an obstacle to scientific and technical advance. As Chandrasekyaran et al. wrote in 2002:

The tradition of open science has eroded considerably over the past quarter century as proprietary claims have reached farther upstream from end

\textsuperscript{59} DoJ (2003), ‘Aventis price fixing’, US Department of Justice, 18 September.

\textsuperscript{60} Anon. (1997), \textit{A Book of Disposable Sayings}, New York: Gardham.
products to cover fundamental discoveries that provide the knowledge base for future product development.\textsuperscript{61}

It is evident that science commonly advances in a series of steps as one innovator continues to build creatively on the achievements of others. An all too broad patent around an invention may therefore block entirely for a considerable period any attempt by other scientists to move further ahead in the same direction.

\section*{6.2.6 The "Evergreening" of Patents\textsuperscript{62}}

While debate around the TRIPS agreement has continued, controversy has also arisen regarding the various attempts made by the research-based industry to extend patent protection for its products. If an ageing patent is due to expire, leading to the advent of competition and hence much reduced prices, a prospect attractive to all parties would be the introduction of a successor drug that is more efficacious or safer. Provided this indeed constitutes a significant innovation of importance in health terms this could be considered defensible. However, a manufacturer may well find that it will not be able to identify and develop a superior product in good time. It may then seek to persuade the authorities to grant it a patent extension on the original drug, falling back on what has been called a semi-innovative or pseudo-innovative approach.\textsuperscript{63} Instead of taking a true step ahead, a sideways step is taken. Some pharmaceutical companies have become remarkably astute at obtaining patents for modifications that may be scientifically and medically insignificant but are at least new. If one can spin a suggestive story around such a slight modification, this may prove sufficient to sell it for a further period at the price of the original, if not more. In some cases the ploy has succeeded.

The Schering-Plough company secured during the 1990s with its product Claritin\textsuperscript{R} (loratidine) a dominant place in the US market for antihistamines for the treatment of allergies. Loratidine was, according to

\textsuperscript{61} Quoted by Chandrasekyaran S, S Kumar, C Valley and A Rai (2009), ‘Proprietary science, open science and the role of patent disclosure: the case of zinc-finger proteins’, \textit{Nature Biotechnology}, 27, 140--44.


the standard reference works, generally similar to other second-generation antihistamines, but an advertising campaign of unequalled proportions led to sales that came to account for a substantial part of the firm’s turnover and growth. With the knowledge that a generic competitor could well afford to sell the drug for a tenth of the price, and with the approaching expiry of the patent in late 2002, Schering-Plough initially sought to get the latter extended; this was unsuccessful, despite what the press described as “millions spent on lobbying”. Without a patented successor capable of providing sufficient real benefit to inherit the market, the firm resorted to obtaining a licence for a metabolite of loratidine that would have essentially the same properties but could be claimed to be different. The metabolite, desloratidine (ClarinexR), was introduced with the same massive though amorphous publicity that had turned Claritin into a best-seller, and it enabled Schering-Plough to retain a substantial share of the high-cost antihistamine market despite the fact that the newness of the product provided nothing in the way of genuine medical innovation.

In 2001, with patents on its anti-ulcer drug omeprazole (LosecR) approaching expiry, and generics likely to appear, AstraZeneca adopted a novel approach to maintain its grip on the high-priced market. Omeprazole was an enantiomer (i.e. a mixture of the laevo- and dextrorotatory forms of the molecule). It now rapidly developed the levorotatory form with its own chemical name (esomeprazole) and the trade name NexiumR, at some ten times the price of the original drug. It was in no sense better than omeprazole nor significantly different from it. As Scott has pointed out, a study designed to prove the superiority of esomeprazole was one in which 40 mg of the drug was misleadingly compared with a mere 20 mg of omeprazole. However superiority was claimed and the drug was invested with its own patent. Goldacre has summarized subsequent events:

The direct-to-consumer campaign in the US was vast: AstraZeneca spent $250 million on ads in 200369 and ... its website to promote the drug eventually pulled over a million visitors every quarter ... Thomas Scully, the head of Medicare and Medicaid, gave speeches explaining that the drug was a waste of money; but with no final control over what gets prescribed in the two organisations, he sat and watched as they spent $800 million on this vastly expensive drug every year ...70

Sometimes the patent attorneys of the originator firm will set out to build a network of new patents around an older drug without it being clear that there has been any real innovation at all; the novelty seems to lie primarily in the ingenuity exercised in redefining the patented area so as to extend its scope and the duration of protection. Even should such patent applications ultimately fail, the proceedings around them may be sufficient to delay the arrival of a generic competitor, as the Apotex case illustrates. In March 1998, Apotex filed an Abridged New Drug Application to market a generic version of the GSK drug Paxil (the antidepressant paroxetine hydrochloride) in the United States. GSK sued Apotex for infringement of its patent, resulting in a 30-month stay, which expired in November 2000. However, by that time GSK had listed eight additional patents and on the basis of these proceeded to bring further successive infringement suits against Apotex, creating a further stay on FDA assessment.71

In 2002, with the approaching expiry of the patent on Pfizer's Lipitor®, a cholesterol-lowering drug based on the calcium salt of atorvastin, the firm obtained patents for various chemical and physical forms of the compound and these were able to provide protection up to 2016.72

It was only to be expected that in due course such attempts to delay or obstruct the marketing of low-cost generics would encounter opposition. When in 2009 the English Court of Appeal dealt with this type of issue in a case involving the Servier company and the generic manufacturer Apotex, it sided very much with a generic applicant who challenged a dubious patent extension. To cite the Court literally:

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72 Hutchins M (2003), 'Extending the monopoly – how "secondary patents" can be used to delay or prevent generic competition upon expiry of the basic product patent', J. Gener. Med. 1(1), 57–71.
... It is the sort of patent which can give the patent system a bad name ... the only solution to this type of undesirable patent is a rapid and efficient method for obtaining its revocation. Then it can be got rid of before it does too much harm to the public interest.73

The Court went on to award Apotex compensation to the tune of £17.5 million against Servier for loss of sales. The judge added that he might have been willing to grant a further award of restitutionary damages had these been requested.74

A very significant judgment in this connection was that of the Indian Supreme Court in April 2013. It was hailed in the literature as “A victory for global public health”.75 In 2006, the Indian Patent Office rejected a patent application by Novartis for the beta crystalline form of imatinib mesylate, marketed as GlivecR or GleevecR, and used to treat chronic myeloid leukaemia. The original form of the drug had been invented prior to 1995, at a time when India did not grant product patents. Novartis appealed the decision. After a prolonged battle in the Indian courts, the Supreme Court of India, on 1 April 2013, confirmed that the patent application failed to meet the requirements for patentability under Indian law. Although the Indian judgment has been severely criticized by industry, the US Chamber of Commerce and others, an authoritative commentator has noted that it is “well-crafted, with close attention to the facts presented, and appears to take a balanced view of the matters brought before the Court”.

Whether the development of a long-acting form of a drug justifies the granting of a secondary patent so that an originator company can in effect extend its monopoly in the market appears to depend very much on the circumstances of the case. There are situations in which it is medically helpful to develop a long-acting form of a known drug, but others in which it is not; judgments on this matter in Britain’s Patents Court have gone in different directions.76

73 Burdon M and R Singleton (2009), ‘Court assesses compensation payable to a generic company unfairly kept off the market’, *J. Gener. Medicines*, 6, 163.

74 Ibid.


As of 2014 there is some evidence that, in both Europe and the United States the tide is turning against "evergreening" and similar means of misusing the patent system to exclude or delay competition. In June 2011 the UK government launched a lawsuit claiming £220 million in damages against Servier Laboratories, alleging that the French pharmaceutical company had "abused" its dominant position by causing a delay to rivals that wanted to launch their own generic versions of the hypotensive drug perindopril. 77 Servier was charged with attempting to enforce an invalid patent "through actual and/or threatened legal proceedings" against actual or potential competitors, as well as paying certain other companies large sums in return for agreements not to supply the UK market with perindopril. The case was brought on behalf of the Secretary of State for Health and a large number of primary care trusts, claiming that over a six-year period Servier had, by obstructing generic competition, forced the National Health Service to pay "elevated prices" for the product.

On the same matter, but on the basis of other legal provisions, the European Commission announced in July 2012 that it had sent a statement of objections to Servier on two counts. In the first place, Servier had acquired scarce competing technologies to produce perindopril, thereby rendering generic market entry more difficult or delaying it; in the second place, Servier had induced its generic competitors to enter into patent settlements in order to protect its market exclusivity. This behaviour might infringe the prohibition against restrictive business practices and abuse of a dominant position (set out in Articles 101 and 102 of the Treaty on the Functioning of the European Union) and could lead to prohibition of this conduct and a fine of up to 10 per cent of each infringing company’s annual worldwide turnover. 78

In the United States there have been somewhat similar developments, but with respect to regulatory provisions rather than patent law. An American originator company has sometimes used a "citizen petition" to assert that approval by the FDA of an abbreviated new drug application for a generic copy of one of its drugs would raise significant public health concerns. The generic industry has accused the research-based firms of misusing this procedure to delay the marketing of its products. In the autumn of 2007, therefore, clauses in a new Act of Congress precluded the FDA from delaying approval of a generic equivalent on the

grounds of a citizen petition unless there was evidence that such a delay was necessary to protect public health; the Agency would be required to take a decision on a citizen petition within 180 days. To date, discussion on the effective implementation of the new rules continues.79

6.2.7 Suppression of Discoveries

From time to time, extreme critics of the pharmaceutical industry have asserted that it has been guilty of suppressing or impeding beneficial discoveries which, if exploited, could run contrary to its commercial interests. A particularly persistent view has been that one or more manufacturers of H₂-blockers, used in the long-term treatment of peptic ulcer, sought for a time to counter the acceptance of research findings showing that such ulcers and related conditions were ascribable to localized infection with the microorganism *Helibacter Pylori* that could readily be eliminated using antibiotic therapy.80,81 The truth appears to have been considerably more subtle. A series of investigations have indeed identified some unclear association between the microorganism and peptic ulcer, though only a small proportion of the individuals with the infection ever develop ulcerous complications, and in some respects *H. Pylori* may actually exert a protective effect. Specialists using H₂-blockers were indeed, and perhaps rightly, critical of optimistic early reports suggesting that a new and low-cost approach to the treatment of peptic ulcer had been identified. It would seem dubious whether any pharmaceutical firm would or could suppress evidence of a new therapeutic approach to a common disorder; more probably it would attempt to adopt and exploit it.

6.2.8 Patents on Biologicals and Biosimilars

The discussion of biologicals and biosimilars has sometimes been confused because of a lack of clarity regarding that field as a whole. Biological medicines, as opposed to the small-molecule chemical products created and synthesized in the laboratory and up to the present used much more widely in medicine, are essentially compounds identical to

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81 Ibid.
natural physiological substances. They are primarily large-molecule compounds such as insulin, erythropoietin, growth hormone and granulocyte colony-stimulating factors. Unlike chemical medicines, biological medicines are prepared industrially in living cells (bacteria, yeast, animal or human cell lines). Although in principle a patent cannot be granted for a product obtained from nature (e.g. insulin obtained from bovine cadavers), patents have for several decades been conferred and marketing licences issued on those created industrially. The novelty lies here in the fact that, generally using recombinant DNA technology, it is today possible to produce substances that are either identical to the natural substance or so close to it that they share all the same properties.

With the progressive expiry of patents on the first generation of such biological products dating from the 1980s, generic competitors should in theory be able to produce and market copies of them, as is the case with synthetic pharmaceuticals. In practice, however, since these firms will have no access to the cell-line used by the original manufacturer, they will be obliged to develop their own. The resultant product is therefore highly unlikely to be absolutely identical in structure to the original though it may possess the same essential properties. It will be regarded as a "biosimilar" and questions will need to be answered as to whether its use, efficacy and safety are sufficiently similar to those of the original to justify its introduction. Patents can be issued for biosimilars, but approval for marketing will require the submission of a well-documented file. Specific legislation to handle the issue is currently in force or under discussion in many countries and the European Union has already approved a number of products of this type. Still controversial is the question as to how a regulatory agency can assess the degree of similarity between the new and the older product and discuss this with the new applicant without revealing to the latter the "trade secrets" already in its possession concerning the manufacture of the original.

Because of the complexity of their structure and of the sophisticated mode of production with recombinant DNA technology, biologicals have until recently been rather less exposed to generic imitation than have synthetic chemicals, and it has been possible to maintain high prices for a long period. A steadily wider group of laboratories and corporations are however becoming familiar with the techniques involved and competition will undoubtedly grow. Since a number of these products are life-saving, this is in the interest of the community. As the field grows, economic practice (and malpractice?) will no doubt mimic ever more closely practice in the field of chemically synthesized medicines.

6.2.9 Data Exclusivity and Monopoly Rights

The drive to secure monopoly positions does not begin or end with patents. Particularly where a drug’s patent protection is not rock solid or has only a short time to run, pharmaceutical companies have in recent years sought to protect it by recourse to claims of “data exclusivity”. The product’s place on the market has after all been earned by the successful submission to regulatory authorities of reports on the studies that the originator company has carried out to demonstrate its efficacy and safety; and except insofar as these reports have also been published in the journals, they are to be found only in the closed archives of these authorities, which are normally bound to regard them as confidential. Companies have therefore argued that these files, having served their original purpose, cannot be rightfully used in the agency’s dealings with any other applicant. If one takes the argument literally, it would mean that, even after the patent has expired, the regulators could not make use of the knowledge that they have drawn from these files to approve any other drug product, even if it is identical. The producer of a generic equivalent 50 years hence might therefore still find itself obliged to carry out once more all the human and animal studies performed earlier with the original product. In that case the cost of introducing a generic equivalent would be prohibitively increased and the originator firm would retain its lucrative monopoly virtually in perpetuity.

It has indeed long been accepted that regulatory bodies should regard data in their files as confidential, the primary purpose of this rule being to protect a firm’s commercial secrets from being viewed by potential competitors. From the early days of comprehensive regulation, however, it was clear that in the public interest some limits might need to be imposed on the confidentiality principle. In assessing a public health crisis relating to a medicine, for example, an agency would necessarily consider itself at liberty to make use of all the relevant knowledge and
experience it had acquired from dealing with past applicants; it could hardly obliterate these things from its memory. It was also obvious that after a drug had been on the market for some years its efficacy and safety would have been confirmed and indeed expanded by practical experience in the field; at that time the original research work would hence no longer be of any interest, having been bypassed by events. It became widely accepted that a secondary applicant at this time could base its submission on “bibliographic data”: the originator’s monopoly would in fact have evaporated. This principle was incorporated literally in the regulations developed by the European Community from 1965 onwards. All the same, faced during the next two decades with emphatic arguments and political pressure from the drug industry to provide data protection, and feeling in addition some considerable sympathy with an industry that at the time seemed to be innovating so successfully, and exporting so profitably to the rest of the world, it was considered “advisable” to seek an arbitrary compromise. It could, after all, prove difficult to identify the point in time at which a particular drug became so well accepted that no further exploratory research could reasonably be demanded when a new brand presented itself. A compromise position was indeed adopted, in the face of indignant opposition from parties concerned about the level of drug prices and the need for generic competition. In essence the policy to be adopted would guarantee data exclusivity for a limited number of years after the originator’s product had entered the market.

When in 1986 new European legislation was enacted it provided, as an element buried in some convoluted phraseology, that when seeking a licence for a secondary version of the drug the applicant could indeed, in lieu of providing new scientific data, show that its product was “essentially similar” to a product that had already been registered. However, that procedure would only operate where the original product had been registered for six years or more; a period of ten years would apply where “high technology medicinal products” (87/21/EEC) were concerned or where a member state considered that the ten-year period was required in the interests of public health. The clause did not provide industry with everything it had sought; in particular, the period of protection was not, except under very particular circumstances, to be extended beyond six years if this would carry protection beyond the validity of the patent. Member states did however retain some freedom in the matter, and most

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85 Directive 65/65/EEC.
86 Council Directive 87/21/EEC.
of the larger states, with substantial interests in drug manufacturing, in fact chose the ten-year option for the protection of data.

Still dissatisfied, industry sought further protection of its data by recourse to the courts. In Britain in 1987, Smith Kline & French Laboratories Ltd (SKF) took legal action to prevent the British regulatory authorities from allowing others to use their data on TagametR (cimetidine) even after expiry of the ten-year period. The drug had been marketed in 1976 and although its 1972 patent was valid for 20 years, it permitted other parties to obtain a licence after 1988. The court of first instance granted a restraining order against the agency, but its decision was overturned in the House of Lords.87 In the view of the Law Lords:

It is essential for the licensing authority to compare the applications of the first and subsequent applicants in order to satisfy themselves that both products are similar, safe, effective and reliable. The licensing authority cannot discharge its duty to safeguard the health of the nation and its duty to act fairly and equally between the applicants without having recourse to all the information available to the licensing authority, confidential or otherwise ...88

Their Lordships indeed went on to suggest that use of regulatory procedures to obtain protection from imitation amounted to misuse of the system. The ultimate consequence was therefore that the two generic producers involved in the case were allowed to rely for their application on the evidence submitted earlier by SKF in order to obtain a product licence for cimetidine.

In 2000, the European Union introduced an additional level of data protection for “orphan drugs” as a means of stimulating innovation in that field. Where a product has been designated an orphan drug, no ‘similar’ product can in principle be registered for the same indication for a period of ten years; the ten-year period of exclusivity can however be reduced to six under certain circumstances. The period of protection could, to quote the original Directive:

... be reduced to six years if, at the end of the fifth year, it is established, in respect of the medicinal product concerned, that the criteria laid down in Article 3 are no longer met, inter alia, where it is shown on the basis of

87 R v. Licensing Authority ex p Smith Kline (H.L.) (1990 1 a.c. 64).
available evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity ... 89

A number of orphan drugs have been registered under this provision, but it is still, as of 2014, too early to determine its ultimate effects either in terms of innovation or exclusivity.

It may be noted that in the United States, where the industry had at one time argued for permanent protection of its data, the FDA did for a time from 1962 onwards almost consistently hold that generic applicants must submit complete scientific files. However, data on the testing of antibiotics and additives were fully disclosed; and learned authors protested at the notion of duplicate investigations for drugs of other types. Ultimately the matter was taken up in the Drug Price Competition and Patent Term Restoration Act (the "Hatch-Waxman Act") of 1984. This introduced the concept of Abbreviated New Drug Applications for generic drugs, for which an applicant could refer the agency to its files on a drug already approved rather than submitting entirely new data.

At the global level the issue of data exclusivity only came into sharp focus in negotiations under the auspices of the World Trade Organization for what ultimately became the TRIPS agreement (discussed in Section 6.2.1 above). After an acrimonious debate, the final text of TRIPS, strongly influenced by the United States and the European Community, included a clause 39.3 which rendered exclusivity of regulatory data compulsory, though in terms which in part (and no doubt on purpose) remained unclear. Data submitted to obtain approval for the marketing of an original medicine were (for an unspecified period) to be protected against disclosure "... except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use". Twenty years after the signing of TRIPS it remains uncertain how these conditions will in the long run be interpreted. The principle of data exclusivity has thus in principle been accepted officially worldwide but in a manner that appears to leave much room for controversy and perhaps further adjustment.

6.2.10 Transfer Pricing 90

Corporations trading internationally in any sector of business frequently transfer goods and services between two countries indirectly, for example

89 Regulation 141/2000 EEC.
via a daughter company in a third country. In such a situation, the transfer prices charged in each phase can be adjusted in the corporation’s favour. The procedure can be used or misused both to justify a high retail price in the ultimate recipient country and to evade taxes. Companies that are clever can attain both objectives simultaneously. To this end, the exporter can supply the product at a very modest price to the intermediate transfer point, situated in an environment where corporate taxes are very low; it will then be sold at a much higher price to the country where it is to be retailed. The parent corporation will therefore take a substantial profit through its daughter company in the low-tax haven, and little or none in the ultimate high-tax environment. Its subsidiary in the latter country will be able to document the fact that it has been obliged to purchase the goods at a high price and is therefore forced to retail it at a similarly high price, while earning very little or nothing on the deal. This ingenious game can deliver high prices, high profits and low taxes worldwide.

Manipulation of prices in this manner is not only common — and notably widespread in the pharmaceutical industry⁹¹,⁹² — but is regarded within corporations as justifiable. It is clear, however, that both the evasion of corporate taxes and the artificial justification of excessively high retail prices in this manner are criminal offences in many countries. Legal proceedings to impose penalties for improper practice have generally related to illegal tax avoidance in the country for which the product is destined rather than to overpricing in the latter.

When the transfer pricing policies of GlaxoSmithKline over the period 1989 to 1996 were scrutinized, US tax authorities concluded that the rate which the company charged for marketing services supplied by its US affiliate had been far too low, and thus understated Glaxo’s US income, hence avoiding payment of some $5.2 billion in US taxes. After litigation and negotiations over 17 years, Glaxo settled the dispute by making a payment of $3.4 billion.⁹³ However by 2009 the company was involved in further dispute with the tax authorities relating to a sum of $1.9 billion.⁹⁴

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Since freedom to set transfer prices is so widely regarded as a normal feature of international commerce, it seems highly unlikely that lawmakers will ever eliminate it completely; the law will however constantly attempt to define limits to the practice so as to prevent gross abuse. What has been termed an "international offensive" to this end is currently under way.\(^9\) Accounting firms advising corporations in this field similarly recognize the method as a familiar aspect of commercial practice, but seek to assist their clients in designing transfer pricing tactics that will not bring them into conflict with the law.

6.3 DISCREDITING OR OBSTRUCTING GENERIC COMPETITION

As is evident from the material presented above, a major originator corporation faced with approaching expiry of a patent on a profitable medicine may go to considerable lengths to prevent or delay the arrival on the market of a low-cost generic competitor. The methods range from the broadening or evergreening of the original patent to claims of data exclusivity. If all else fails, the original patent holder may simply set out to discredit the generic product in the eyes of the authorities, the health professions or the public.

The bulk of the generic products marketed internationally have passed the critical filter of modern drug regulation and are entirely respectable. However, from some of the information disseminated by the research industry on this score one would not think so; they are portrayed, explicitly or by implication, as being ineffective, dangerous or at least untrustworthy. One recalls an article on generics in the *Economist* in the 1980s. Slanted heavily towards the arguments of big pharma, the article was illustrated with a photograph of what appeared to be a garden shed, apparently intended to suggest that it was under these conditions that generic medicines were being manufactured. Not every item with this bearing was so subtle. Particularly in the early years of the shift towards generics, some research-based firms tackled them aggressively. A single example is cited in the next paragraph.

In 1986 Ayerst Laboratories in the United States was faced with approaching expiry of its drug Inderal\(^R\) (propranolol). The company therefore indoctrinated its sales force with a "sales simulation" videotape.

It showed a representative explaining to a physician that patients on Inderal “are high-risk patients”, who “need Inderal’s proven therapeutic efficacy”. With a generic version of propranolol, the doctor was told, “there’s always the chance that patient response may be compromised”.

At the same time, Ayerst sent out “Dear Pharmacist” letters, discussing a pharmacist’s “potential liability” if generic propranolol were dispensed instead of Inderal and something went wrong. The letter warned of “troublesome and expensive” lawsuits that would “generate adverse publicity”. The letter was subsequently found by the Food and Drug Administration to be false and misleading by virtue of its “suggesting unknown perils”.

How effective such untruthful efforts to disparage generics nevertheless could be for a time became evident as patients themselves began to become wary of generic substitutes for the “branded” product. During street interviews conducted by a health team in Kampala, Uganda in 1994, the interviewers encountered a married couple who declared that they had scarcely eaten for a week because their baby boy was ill and they were obliged to pay for a branded antibiotic. When reminded that the same antibiotic was available free of charge in generic form at the university clinic, they answered that they had been assured that “the real thing” was much better and essential to the child’s recovery. This is an awful and powerful story.

Payments to desist is another ethically disturbing practice. On occasion, an originator firm faced with the prospect of losing highly profitable sales to a low-cost generic version of its drug, may have recourse to what essentially constitutes bribery to dissuade a potential competitor from entering the market. The practice has in the United States been the subject of court decisions, turning on the question as to whether it violates antitrust law. The circuit courts have been split on the issue, but in 2008 the Court of Appeals for the Federal Circuit took the view that in a case involving Bayer there was not a breach of the law. In 1992 Germany’s Bayer AG, together with the Bayer Corporation, brought suit in the United States against Barr Laboratories, a generic drug company, after the latter had submitted to the FDA an abbreviated new drug application for its generic version of Bayer’s antibiotic ciprofloxacin. In 1996 Bayer entered into settlement talks with Barr and an associated

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company; an agreement was reached according to one section of which Barr would delay the introduction of its own product. In exchange, Bayer agreed to pay Barr the sum of $49.1 million. The agreement became the subject of an antitrust suit brought by advocacy groups and by direct and indirect buyers of brand-name ciprofloxacin. A district court held that such an agreement was not per se a violation of antitrust law since in this case the anticompetitive effects caused by the settlement were within the exclusionary zone of the patent and thus could not be redressed by federal antitrust law. The decision was affirmed by the Court of Appeals.98

The decision in this particular case seems to have turned on details of the patent on the one hand and the inter-company agreement on the other; it is not clear whether similar agreements in other cases will be tolerated; advocacy groups and drug funding agencies are clearly strongly opposed to them and seem likely to continue sponsoring antitrust litigation.

Such agreements are however to date far from having been suppressed in other markets. In April 2013 Britain’s Office of Fair Trading accused GlaxoSmithKline of market “abuse”, having paid rivals to delay the introduction of their own version of GSK’s paroxetine (Seroxat®). Alpharma, Generics UK and Norton Healthcare had, according to the OFT, all received money not to enter the market with their paroxetine. GSK claimed that the agreements in question had been terminated in 2004; at the time of writing, the Office of Fair Trading was preparing to decide whether or not competition law had been infringed.99

In a complaint brought by America’s Federal Trade Commission (FTC) against Bristol-Myers Squibb, the firm was charged with malpractice of this type in seeking to protect its annual sales of nearly $2 billion in two anti-cancer drugs based on paclitaxel and its anti-anxiety product Bu-Spar® (buspirone). One element in the complaint related to Bristol allegedly having paid the producer of the generic equivalent of Bu-Spar a sum exceeding $70 million to delay the introduction of its competitive product. Bristol had also signed agreements with other firms to share monopoly profits and had filed baseless patent infringement lawsuits to delay entry by generics. In addition the firm had allegedly sought to postpone the onset of generic competition to its products by what the FTC termed “abusing governmental regulatory processes”.

98 Majiduddin FK and PA Braier (2009), ‘Recent cases highlight shortcomings and inconsistencies in the law: In re Ciprofloxacin; Celgene v KV and SB Pharmco v Mutual’, J. Gener. Medicines, 6, 167–75.
Under the Hatch-Waxman Act of 1984, which governs FDA approval of generic drugs, a brand-name company seeking to delay generic competition can submit to the FDA information on certain types of patents relating to its product. The FDA lists the approved drug and its related patents in a publication referred to as the “Orange Book”. Once a patent is listed in this book, any firm seeking to market a generic equivalent prior to patent expiration must submit evidence to the FDA that the patents listed in the Orange Book either are invalid or will not be infringed by the proposed generic. If the patent holder files a patent infringement suit within 45 days of this notification, FDA approval to market the generic drug is automatically stayed for 30 months, regardless of the merits of the suit, unless before that time the patent expires or a court holds that the patent is invalid or not infringed. The statute allows listing only if: (1) the patent “claims the drug or a method of using the drug”; and (2) the patent is one “with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug”.

In the matter in question, BMS was stated to have submitted patents for inclusion in the Orange Book which did not meet these criteria. The company was also sued in this matter by state attorneys general to recover monetary damages. The upshot of the FDA complaint was that Bristol-Myers Squibb signed a consent order with the FTC. Among other provisions, the order eliminated Bristol’s ability to obtain a 30-month stay on later-listed patents or where Bristol had engaged in certain types of misconduct in connection with obtaining and listing a patent. The company was further placed under the oversight of a monitor appointed by the US Attorney in New Jersey: the individual states incorporated closely similar injunctive terms in their own orders with the firm, and in addition recovered substantial monetary relief.100

Practices of this type nevertheless are alleged to continue. As of October 2012 the US Supreme Court was reviewing a case in which the Solvay company had been found to have paid substantial sums to three generic firms to delay the introduction of products that would compete with Solvay’s highly profitable testosterone product AndroGel. Lower courts had found that the acts were not anticompetitive, a ruling contested by the Federal Trade Commission.101

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In such a situation it is not necessarily the originator of the product that takes the initiative to pay a potential generic competitor to keep its distance for a while; a generic firm may actually solicit what is essentially a lucrative bribe from the patent holder. The above case, and the signing of the consent order, had an unusual sequel for Bristol-Myers Squibb. In 2006 the firm drew up a draft agreement with Apotex under one clause of which it was agreed that Bristol itself would not market a generic version of Plavix\textsuperscript{R} (clopidogrel) in America so that Apotex could for a period enjoy a generic monopoly. Under the Consent Order already signed with the FTC, any such marketing agreement had to be submitted to the Commission which would advise whether it was anticompetitive or not. BMS duly submitted it to the FTC, which responded by posing a number of incisive questions. Bristol immediately withdrew the draft and in its place submitted another one in which no reference was made to BMS not marketing a generic version of Plavix. In fact, however, Dr Andrew Bodnar, a vice-president of BMS, had in the meantime agreed orally with Apotex that Bristol would not market its generic. In due course, when examining papers submitted by Apotex, the FTC discovered the existence of this concealed oral agreement and the matter was referred to the United States District Court for the District of Columbia. In 2009 the Court sentenced Dr Bodnar to a fine of $5,000 and two years’ probation. In addition, as a report in the New York Times put it, the judge ordered Dr Bodnar to write a book cautioning other pharmaceutical executives not to lie to the FTC!\textsuperscript{102,103}

In July 2006 the Federal Bureau of Investigation had raided the company’s corporate offices in connection with the distribution of Plavix and charges of collusion.\textsuperscript{104} On 12 September 2006, the monitor, former Federal Judge Frederick B. Lacey, urged the company to remove its CEO


Peter Dolan over the Plavix dispute. Later that day, BMS announced that Dolan would indeed step down.\textsuperscript{105}

Finally, a major producer may have recourse to the courts to challenge as essentially unjust a marketing licence that has been awarded to a generic or secondary firm. In the case of life-saving drug Taxol\textsuperscript{R}, the research history of which was sketched in Section 6.1.4 above, one of the steps ultimately taken by Bristol-Myers Squibb to block the marketing of an affordable generic equivalent was to challenge as unjust the Netherlands marketing licence already granted to a small European firm. The case was argued before a court in the Netherlands in 1997–8, where BMS sought to prevent the smaller firm, based in the Netherlands and Norway, from holding a marketing licence for what was an essentially identical product that nevertheless promised to be available at one-tenth of the BMS price. Here too, as it had done in the United States, BMS stressed to the court its need to recover the substantial costs that it claimed to have incurred in research and development; the essential role in fact played by US public funding in the drug’s discovery was not mentioned. The court duly annulled the marketing licence already awarded to the generic company, apparently citing in its judgment "... the importance of preserving the law's incentives for conducting medical research".

One must add however that BMS was shortly afterwards reported to have made assurance doubly sure by purchasing the generic firm concerned in order to remove the threat to its own income.\textsuperscript{106}

\section*{6.4 OPPOSITION TO PARALLEL IMPORTS}

One can have some sympathy with the industry’s efforts to discourage parallel imports, i.e. the importation of the original drug from a market where it is available more cheaply. To a degree, it is only fair that retail prices vary somewhat between countries so that less wealthy populations contribute less to a firm’s costs and profits than do those elsewhere; parallel importation undermines this practice, and it may in extreme cases deprive poor populations of much-needed items and disproportionately enrich unproductive middlemen. It is hardly possible to argue that items so imported are of a lesser standard, though for reasons of availability


\textsuperscript{106} Dukes MNG (1998) (Expert witness for the defence), Notes on proceedings before District Court of Utrecht. See also: Markandya and Love, ‘Timeline of Paclitaxel disputes’, op. cit.
they may differ to some extent in the excipients employed. It is important here to find a policy balance, so that all parties are treated fairly.

Similarly, discrediting personal imports from low-cost markets became a prominent activity in the United States with the realization that because of official controls the prices of most drug products were substantially lower across the Canadian border than at home, as noted in Section 6.1.4 above. Far from reducing US prices in response, the pharmaceutical industry sought to suggest – and induced politicians to fear – that drugs purchased over the border were less trustworthy than those bought in the United States, the suggestion being that they could have been contaminated or might in fact prove to be ineffective counterfeits. Instilling a distrust of "foreign" drugs into society has some justification where one is dealing with medicines acquired from suspect sources or on the internet, but it hardly applies to Canada.107

6.5 ADMINISTRATIVE, CIVIL AND CRIMINAL LIABILITY

6.5.1 Rules, Sanctions, Penalties and Settlements

The duties incumbent on a pharmaceutical company where issues of cost and pricing are concerned are not issues only of patent law or of national pricing edicts. The machinery of justice takes various forms and any or all of them may be brought to bear. Instruments of administrative and social law include legislation applicable to business as a whole (for example patent law) and that specifically governing the selling and pricing of medicines. The civil law defines the relationship between parties whether general (the law of tort) or specific (the law of contract). The criminal law lays down behavioural standards so fundamental to the functioning of the community that failure to adhere to them is likely to incur severe punitive measures.

In a given situation, any or all of these forms of law may come into play. An individual or institution that has behaved improperly may be fined for contravening an administrative rule, but at the same time obliged to pay civil damages to a party injured by the act in question and in the extreme case sentenced before a criminal court.

One must note that, for a long period in history, criminal charges were brought only against individuals. As Friedrichs has pointed out, "The corporate empires of the robber barons... of the second half of the nineteenth century... were largely invulnerable to legal controls".\textsuperscript{108} It became increasingly clear, however, with large corporations becoming an ever more dominant element in society, that their activities would have to be compatible with the interests of the community as a whole, and that where they failed to meet that standard they must be called to account. Clinard and Quinney, who were among the first to use the term "corporate crime", provided a classic definition in 1973.\textsuperscript{109} In cases of corporate offences, society has generally chosen to impose penalties in the form of fines payable by corporations; however, even massive fines imposed on a wealthy corporation may be dismissed as mere business expenses, and will in that case hardly function as a deterrent. A corporation will in any case often agree to settle a case financially, so that its guilt may go largely unnoticed. Only sporadically has society in recent years sought to identify and pass sentence on the individuals within a corporation who caused an offence to be committed or failed to prevent its occurrence.

\subsection{Acceptable and Unacceptable Pricing}

The issue of overpricing was reviewed above (Section 6.2.3) but the question remains as to the point at which excessive pricing of a pharmaceutical constitutes criminal activity.

In a world that has overwhelmingly become the preserve of a free market system, it is generally accepted that prices of consumer goods will be governed primarily by supply and demand. If a corporation sets the prices of its products at too high a level, demand will fall; the customer will either not buy at all or will turn for his supplies to a competitor. This simple principle does not however apply literally in any field of modern commerce, if only because of the extent to which demand can be manipulated by astute advertising and other strategies we have discussed. In the area of pharmaceuticals, the supposedly simple balance of supply and demand is even less in evidence. For one thing, demand is relatively inelastic: illness does, whether one likes it or not, generally demand treatment; and to that extent the seller of a drug holds


the buyer at ransom and can in an affluent market set the price at a level most comfortable for itself. It follows that in many situations the setting of a high price for a medicine will mean that the patient will have no access to it; he or she will have to accept an inferior treatment or none and in consequence may well remain ill or die. Findings such as those cited in Section 6.1 leave one in no doubt that the manufacturers of branded and patented medicines are prone to overprice their products to a serious extent when they have the opportunity to so. It is not the mere fact of price variation that is questioned; to some extent, charging "the price that the market will bear" is socially justifiable and is regarded as sound commercial practice, with the world's wealthiest shouldering the heaviest burdens. What is regarded as immoral and antisocial is the fact that many a worthwhile or even life-saving drug is likely, so long as no cheap generic equivalent is available, to be priced at such a level that it is placed entirely out of the reach of patients and entire populations who need it.

That situation exists even among the less affluent segment of western society; it is seen in much more extreme form in the world's poorest populations in Africa and Asia. In a developing country, too, a multinational corporation may well find that it is considerably more profitable to sell its product at a high price to the relatively accessible affluent minority in the cities than more cheaply to the bulk of the countrywide population where incomes are low and where distribution is troublesome and perhaps relatively costly.

The financial penalties imposed for criminal overpricing have often been severe, though they must always be viewed in relation to the extraordinary sums that may already have been earned. For the company involved, they may be quietly viewed in the boardroom as little more than unavoidable expenses incurred in the process of developing income. In 2003, TAP Pharmaceutical Products agreed to pay a total of $875 million to resolve criminal charges and civil liabilities in connection with its fraudulent drug pricing and marketing of Lupron® (leuprolide), a drug sold primarily for the treatment of advanced prostate cancer. Among other proven charges it had been shown that TAP had defrauded the US government of more than $559 million by filing false and fraudulent claims with the Medicare and Medicaid programmes, by fraudulent drug pricing schemes and by sales and marketing misconduct. The "average wholesale price" reported to Medicare as a basis for claiming payment
had been substantially higher than the price at which the firm had in fact offered the drug to physicians and other customers.\textsuperscript{110}

It may be noted that the entire amount of the criminal fine paid by TAP in the above case was to be transferred to the Department of Justice's Crime Victims Fund, an acknowledgement of the fact that the victims of corporate crime, like those of violence or rape, have a right to compensation by the party responsible for their injury.

As things stand at present, one can often do little more than fight the occasional battle, in the media, in the courts or in both. Barely a year after 39 drug companies had been obliged to retreat from their attempt in the South African courts to challenge the government on drug pricing,\textsuperscript{111} the industry found itself very much on the defensive in that same country and actually risking penalties on a pricing issue. The matter was especially prominent in the public health debate in a society where the prevalence of HIV/AIDS infection was massive. In 2002 a group of individuals and organizations lodged a case against GlaxoSmithKline and Boehringer Ingelheim before South Africa's Competition Commission.\textsuperscript{112} The parties alleged excessive pricing of four AIDS drugs to the detriment of consumers, a practice explicitly prohibited by the country's recently passed Competition Act. In October 2003 the Commission allowed the case and referred the matter to the Competition Tribunal. The latter was requested to allow compulsory licensing of the four products, but also to impose substantial penalties equivalent to 10 per cent of the turnover of these drugs for each year of violation. The firms capitulated and negotiated a settlement involving licensing of the products on very favourable terms to a number of generic producers and granting permission for the latter to export the drug to countries within Sub-Saharan Africa.

In principle, where society is prepared to insist on it, one should be able to counter overcharging. Australia operated for a considerable number of years an excellent pricing scheme that accomplished this, assessing the worth of a new drug to the community in the light of its medical value as compared with that of existing products. New Zealand does so at the time of writing. Alternatively, society should be able to insist on sufficient openness regarding a producer's basic costs and

\textsuperscript{110} PRNewswire (2001), 'TAP Pharmaceutical Products Inc. and seven others charged with health care crimes; company agrees to pay $875 Million to settle charges, reports US Attorney', \textit{PRNewswire}, 3 October.

\textsuperscript{111} See Chapter 4.

\textsuperscript{112} Tau H (2002), Statement of Complaint in terms of Section 49(2)(b) of the Competition Act 89 of 1998.
expenses to assess what constitutes a fair price for his products. Very recently, in response to external pressures, a trend has emerged towards somewhat greater openness on the part of several large pharmaceutical corporations as regards the scientific data that they hold. It is not impossible, given sufficient pressure on behalf of society at large, that a similar degree of openness will be achieved as regards the true costs of drug development and the extent of other justifiable expenses. This could put the community in a better position to assess where fair pricing begins and ends.

6.5.3 The Notion of Industrial Charity

Before setting aside entirely the consideration of acceptable and unacceptable pricing, it is only fair to consider the extent to which the pharmaceutical industry, with its massive earnings, has engaged in charitable acts, especially in the developing world. Philanthropy, it is said, is excellent medicine for the conscience, but it is also a useful tool for boosting one's reputation. It has on occasion been striking to observe the eagerness with which the pharmaceutical industry has, in its public relations efforts, laid the emphasis on its good deeds. As a major player in trade and business, one would also expect it to have the ability to engage in philanthropy from time to time, without harm either to its shareholders or to its own well-being. How far such charitable deeds should be carried is a matter on which the industry itself must decide. In the 1990s, as a US public interest group observed, the drug industry's profitability was almost four times greater than the median for all industries in the Fortune 500 listing (see also the data from later years cited in Section 6.1.3 above). Against this background, any excess of benevolence might well be regarded by industry critics as evidence of an overabundance of riches.

Where the poorer countries of the world are concerned, both individual companies and the industry as a whole have sometimes seemed to attain the golden mean. Pfizer created the Diflucan Partnership in 2000 to provide treatment for two AIDS-related fungal infections in developing countries. Pfizer and its programme partners distribute Diflucan (fluconazole) treatments free of charge to governments and NGOs in

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developing countries. Pfizer also provides materials to support patient education and health care worker training.\textsuperscript{114}

In June 2008 the US Fund for UNICEF and Merck announced the donation and delivery of 100,000 doses of measles, mumps and rubella virus vaccine to the government of the former Soviet republic of Moldova, in response to an ongoing serious mumps outbreak in that country. The CEO of the Fund called the donation "a shining example of corporate goodwill".\textsuperscript{115} In the weeks following the earthquake that demolished the capital of Haiti in January 2010, the American pharmaceutical industry was reported to have offered financial relief to the tune of $35 million.\textsuperscript{116}

Sometimes, on the other hand, the industry's attempts to display a generous streak have been less happy. Charitable organizations and social clubs have erred in sending entirely inappropriate drug supplies to countries in crisis, but in such cases ignorance of the actual needs and of the suitability of particular items may provide an explanation, if not a justification.\textsuperscript{117} Inappropriate donations by pharmaceutical companies are less easy to excuse, especially where for the donor itself they prove to constitute a benefit rather than a sacrifice. In 1996, after the genocide in Rwanda, the Eli Lilly company of Indianapolis sent a very large supply of tablets of the antibiotic Ceclor CD\textsuperscript{R} (cefaclor sustained release). The antibiotic had not yet been licensed for sale in the United States and, as a second-generation cephalosporin, it was not suitable for wide use in the absence of a specific bacteriological diagnosis, nor did it feature in WHO's recommendations on essential drugs needed for refugees. A press release from Lilly referred to the donation as a further example of Lilly's commitment to giving, especially in times of human tragedy ("We are responding to the dire needs of the Rwandan refugees"). There were enough tablets to treat 1.3 million people accompanied by a small

\begin{footnotesize}
\begin{itemize}
\item[116] PHARMA (2010), 'America's Pharmaceutical research companies donate $35 million to relief efforts in Haiti; more help coming', Pharma press release, 23 February.
\end{itemize}
\end{footnotesize}
number of inserts in English as to how they should be used. The firm admitted however that the stock was nearing expiration and as it had not received FDA approval for sale in the United States, the drug was of no use to the firm.\textsuperscript{118} In a case such as this a US firm has a particularly good reason to donate such a drug whether appropriate or not, since tax law enables it to claim a tax rebate not less than double the value of the drug donated. In principle, therefore, Lilly stood to benefit from this dubiously welcome charity.

In the last two decades, examples of such drug dumping by pharmaceutical companies have been numerous. Supplies were sent in this manner to Bosnia and to Armenia during major times of conflict and were found to be useless;\textsuperscript{119} appetite stimulants were donated to a starving refugee population in Sudan, while refugee camps in Albania received ten tons of depilatory (hair removal) cream and another cream for the relief of haemorrhoids.\textsuperscript{120} Donations to Macedonia included garlic capsules and nicotine inhalers.\textsuperscript{121} Dumping of this nature is clearly antisocial and immoral, and it is arguable that where it is not yet frankly illegal it would indeed be right to regard it as such in the future.\textsuperscript{122}

There are however some donations by industry which appear to fall into a very different category and at this point it is proper to take a look at them. Certainly the most widely known instance of an industry donation that has been very widely proclaimed is the long-term programme developed by Merck in partnership with the US Fund for UNICEF to treat and hopefully eradicate onchocerciasis ("river blindness") in West Africa. It merits a particularly close look since its complex story is so abundantly documented and can be viewed from various angles.\textsuperscript{123,124}

\begin{thebibliography}{99}
\bibitem{118} \textit{Time}, 29 April 1996.
\bibitem{119} Thomas M (2002), \textit{Drug Donations: Corporate Charity or Taxpayer Subsidy?}, London: War on Want.
\end{thebibliography}
In 1975, Merck found that the avermectin group of compounds, isolated from a microorganism by a Japanese research group, had antiparasitic activity and ivermectin (in fact a mixture of two related compounds) was introduced to the veterinary market in 1981. By 1995 it was reported that it had attained annual veterinary sales of $740 million. In 1978, the same preparation was found to be effective in human onchocerciasis and it was developed for this purpose with substantial financial support from public international organizations, including WHO’s programme for research on tropical diseases (TDR). In 1987 the company decided to provide it free of charge in the infected areas of Africa, for as long as necessary, the hope being that onchocerciasis could in this way be eliminated. In 2007, over nine million people received treatment with the drug in the framework of the donation programme.

The Merck initiative has been widely lauded, and although at first criticized in the boardrooms of other companies, its example undoubtedly inspired comparable programmes funded by SmithKline Beecham using albendazole and by Pfizer in 1998 using azithromycin to control trachoma in five countries.

All the same one must maintain a sense of proportion in these matters, particularly because while insisting on decency, one is not necessarily demanding great sacrifices. As Roy Vagelos, the CEO of Merck at the time the ivermectin programme was initiated, told a journalist, “The

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130 Tavis, ‘River Blindness: the Merck decision to develop and donate MECTIZAN’, op. cit.
provision of the chemical is a minor side, so it's not a significant cost”.\textsuperscript{131} One must also take into account, as noted earlier, the US government’s generous tax deduction policy for donations: double the drug value plus 75 per cent to cover overheads.\textsuperscript{132} Vagelos estimated that the programme had cost Merck “hundreds of millions of dollars over the years”. That must be set against the earnings of the Merck group as a whole, amounting in 2007 to over $40 billion\textsuperscript{133} and growing yearly, while during the 1990s the corporation’s pure profit on making drugs was stated to be some 44 per cent of earnings.\textsuperscript{134} Viewed in that light, and in view of the benefit flowing from tax reduction and the tremendous boost that the donation gave the firm in terms of public prestige and recruitment, one might perhaps conclude that the river blindness programme constituted an excellent – and extremely economical – financial investment rather than a sacrifice.\textsuperscript{135} Stepping aside from this specific example, it is a plain fact that corporate “generosity” in providing particular drugs at little or no cost to some populations in the developing world tends to be overshadowed by serious overcharging for the same drugs in other areas where something of a market can be identified. The free distribution of the life-saving drug fluconazole by Pfizer, noted above, has been viewed in this light by critics, who noted after the introduction of the programme that at that time the firm was charging $4.15 per tablet to the public health services in South Africa and as much as $18.00 per tablet in Kenya, exceeding the price charged in the United States and putting the treatment entirely out of reach of many who needed it. In Thailand, where a generic form of fluconazole was available, the price per tablet was no more than $0.29.\textsuperscript{136}

\textsuperscript{132} Tavis, ‘River Blindness: the Merck decision to develop and donate MECTIZAN’, op. cit.
\textsuperscript{133} This figure includes the firm’s activities beyond drug manufacturing, notably through its pharmaceutical benefit management company Merck-Medco.
\textsuperscript{135} See also RD Laing (2001) as well as P Saunders (1999), both as quoted by Wehrwein, ‘Pharmacophilanthropy’, op. cit., pp. 3–4.
In summary, all charitable acts, whatever their source, are commendable. Before however cataloguing them as pure evidence of the pharmaceutical industry’s socially responsible comportment, it is only reasonable to set the sums involved against the immeasurably greater sums paid by that same industry in the form of fines and compensation for acts that have been directly contrary to the interests of the community.

Finally, where serious disease is concerned, the fatal flaw in relying to any extent on philanthropy as practised by commercial companies is that it will all too readily be exercised selectively, with corporate management deciding to suit its own convenience who shall benefit and who shall not – who shall live and who shall die.

6.5.4 An Industry/Government Imbalance?

When one examines the behaviour of the pharmaceutical industry as a whole in the community, one is repeatedly struck by the manner in which its attitudes betray what satirists have on occasion termed a “superiority complex”. Backed by very considerable financial means, equipped with a formidable lobbying apparatus and bolstered by repeated successes in manipulating parliament, professionals and the public to its own ends, the pharmaceutical industry appears to have acquired something approaching an ironclad conviction of its own invincibility. However obsequious its public statements regarding other parties may sometimes be, the industry’s acts and the attitudes often fostered within its walls display a degree of underlying contempt for the rest of the world. That contempt may extend to regulatory authorities, to the parties that industry so successfully manipulates (Chapter 4) and to governments, even where the latter have sought to compromise in some way with the industry.

Over a number of years, having regard to the reasonable needs of the research-based industry, Canada progressively limited and then (in 1993) abolished the use of compulsory licensing of medicines, despite the fact that this would inevitably lead to an increase in average market prices. In exchange for these well-meant concessions, the industry promised to increase its R&D activities and create new employment in the sector in Canada. Four years later it was found that these promises had not been fulfilled.\footnote{Lexchin J (1997), ‘After compulsory licensing; coming issues in Canadian pharmaceutical policy and politics’, \textit{Health Policy}, 40(1), 69–80.}
In India, one espies in some matters a similar lack of true respect for public authority. In January 2006 the Indian patent controller rejected an application by Novartis of Switzerland for its anti-leukaemia drug imatinib mesylate (Glivec<sup>R</sup>) on the grounds that it was merely a new form of substance already known, and therefore excluded by the restrictions laid down in the national patent law. The Novartis application had been promptly opposed both by the Cancer Patients Aid Association and by a local firm already selling a generic version of the product at just one-tenth of the Novartis price. In court Novartis now challenged the restrictions on patentability embodied in the Act, claiming that it was contrary to both the TRIPS agreement and the Constitution of India. In August 2007 the Madras High Court rejected the Constitutional claim brought by Novartis, but referred the issue of TRIPS compatibility to the WTO body dealing with the settlement of disputes.<sup>138</sup>

Following this defeat Novartis did not seem at all inclined to abandon its effort to overturn the Indian patent law, despite protests from patient advocacy groups,<sup>139,140</sup> though admitting that the issue was primarily one for the WTO.<sup>141</sup> It seems very likely however that the pharmaceutical industry will continue to challenge both the Doha Declaration and the relevant national laws; but it is equally likely that in these matters it will find itself faced by a vociferous and increasingly confident lobby from civil society, anxious to see patent laws in place which are stronger rather than weaker than that enacted in India.

In February 2012, following a decision by the Bombay High Court that the state had the right to recover sums wrongfully earned by drug companies over a nine-year period, India’s Department of Pharmaceuticals sent notices to more than 500 pharmaceutical companies requiring the submission of data on the basis of which the sums to be

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recovered could be calculated. As of late May 2012 not a single company had responded to the notice.\(^{142}\)

Meanwhile, Hoffmann-La Roche appears to have had no hesitation in defying both the experts and authorities across the world when it appeared to be in its interests to do so. Despite now widely expressed doubts about the efficacy of its product Tamiflu\(^{R}\), stockpiled globally on a vast scale under industry influence at the time of the swine flu epidemic (see Chapter 4), the firm was according to the *British Medical Journal* still unwilling as of October 2012 to release all its clinical data on the matter for impartial evaluation.\(^{143}\)

The creed of invincibility is nowhere more apparent than in the manner in which many a corporation deals with the governments of developing countries, reflecting perhaps the gross discrepancy between the economic strength of corporations and that of governments in this situation (see Table 6.2).

If, in the future, society is to seek to solve the problems that currently involve the industry and arrive at an effective process of restorative justice\(^{144}\) there must necessarily be participation by all the parties involved, on equal terms and characterized by genuine mutual respect. That respect has to be earned by each party and granted by all the others. To date, one must conclude that we have not become sufficiently close to that ideal.

### 6.6 THE HEALTHY INNOVATOR

Any system of rules, however noble its proclaimed purpose, is likely to be subject to misuse by the less noble. The patent system at its best is a means of rewarding merit, but it can also be misused to strangle initiative and deprive many in society of the fruits of the very innovation that it is supposed to promote. Similarly, drug regulatory regimes are designed to ensure that the safest and most effective drugs known are accessible to all; but if these regimes are manipulated in order to preserve monopolies on unnecessarily costly products, they may themselves lead to stagnation and deprivation.

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\(^{142}\) Singh K (2012), ‘Pharma companies unresponsive to overcharging notices’, *Economic Times*, 25 May.

\(^{143}\) AP (2012), ‘Tamiflu scrutinized as BMJ calls on pharmaceutical giant to release data’, *Guardian*, 12 November.

Table 6.2 Corporate turnover of selected pharmaceutical corporations\(^a\) versus gross national product of selected developing countries\(^b\) (billions of dollars annually)

<table>
<thead>
<tr>
<th>Company</th>
<th>Company revenue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer</td>
<td>48.4</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>45.4</td>
</tr>
<tr>
<td>Bayer</td>
<td>44.6</td>
</tr>
<tr>
<td>Hoffman-La Roche</td>
<td>40.3</td>
</tr>
<tr>
<td>Novartis</td>
<td>39.8</td>
</tr>
<tr>
<td>Abbott</td>
<td>25.9</td>
</tr>
<tr>
<td>Merck(^c)</td>
<td>24.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Country</th>
<th>Gross national product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethiopia</td>
<td>11.1</td>
</tr>
<tr>
<td>Uganda</td>
<td>7.9</td>
</tr>
<tr>
<td>Zambia</td>
<td>5.7</td>
</tr>
<tr>
<td>Laos</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Notes:
\(^a\) Cited from Fortune 500 estimates in 2005.
\(^c\) The Merck figure was that quoted prior to its merger with Schering-Plough; the revenue of the combined firm was estimated at about $46.9 billion.

In 1623, as noted above, the English Parliament was obliged to revise drastically a system of monopolies that, once created with the best of intentions, had turned sour. Society at the present day is clearly in need of greater innovation in the field of drug treatment. Could it be that the Doha Declaration indeed represents the thin end of a new trend, gently but persistently nurtured by civil society, to bring about a rethink of the way in which medical advances can best be promoted, without at the same time promoting undue enrichment or rendering access to these advances unaffordable?

That need not involve an abandonment of the patent system as a whole. For centuries, pharmaceuticals were in many countries excluded from the patent regime, and it could be that they indeed merit a distinct system of their own to protect both the innovator and the public interest in a more...
appropriate manner. Jamie Love with his notion of “prizes for achievement”\textsuperscript{145} has been in the forefront of efforts to bring about something of that nature. Others have laid the emphasis on a greater use of publicly funded clinical trials, the creation of a Health Impact Fund pioneered by Thomas Pogge and new means of financing research.\textsuperscript{146} In Part III of this volume we shall look at a number of such proposals in considering how we may be able to map out a better road ahead.

It may seem an impossible challenge to regulate breaches of antimonopoly laws, to crush cartels, to keep a place for patents that grant legal monopolies, to limit the abuses and excessive reach of patent monopolies, to manage evergreening, to balance patents with prizes or health impact funds, to help generic industries thrive, to nurture other new business models that do not rely on patents (such as open-source biotechnology (Chapter 8)), to sustain prices that make it profitable to invent new drugs in developed markets, and prices that make it possible to supply medicines to the poorest people of poor countries, to mobilize both private philanthropy and state philanthropy to that end, to increase transfer prices that are so low as to eliminate tax liability and reduce those that are so high as to justify exorbitant prices under public pharmaceutical benefits schemes, to mobilize criminal law, administrative law and civil law in melding all of these objectives. Impossible it may seem, but we believe it can be done. Our objective at the end of this book is to outline the principles, if not the details, which must vary greatly by local context, of a policy mix for an integrated regulatory approach. This approach shows how it is possible to pursue an integrated optimization of all those seemingly contradictory objectives.


PART III

Transforming the way ahead
7. A criminological perspective on a worsening crisis

7.1 LOOKING TO THE FUTURE

In opening Part III of this volume, the present chapter provides an overview of ten themes and patterns that came to the fore in Part II. It then takes these as a foundation for a distinctively criminological perspective on the problems surrounding the pharmaceutical industry. Chapter 8 goes on to examine the case for and against criminal enforcement as an element in an integrated reform strategy. Criminalization, we argue, can be overused, and even where there is a case for criminalizing a particular type of wrongdoing, it is often better to appeal to the ethics of the industry as a tool for righting wrongs than to incarcerate felons. The argument of Chapters 8 and 9 is that by resisting the temptation to crowd out corporate ethics with excessive criminalization, we can actually be more effective in reducing corporate crime in the pharmaceutical industry. Chapter 10 argues for a partial privatization of enforcement and for restorative justice dialogue between industry and its critics as ingredients of change. Finally, Chapter 11 argues that nothing less than a new capitalism and a new drug diplomacy are needed. Corporate crime in the pharmaceutical industry can have a catalytic role in helping us to glimpse something of a largely unpredictable future.

This book identifies many and various kinds of abuses by the pharmaceutical industry. A very large web of disparate complementary controls and supports is needed in response. We argue, with many illustrations, for a wide plurality of criminological and non-criminological strategies to control corporate crime in the pharmaceutical industry. Yet Part III is not a comprehensive analysis of the pros and cons of all the strategies that are important. Rather, it seeks to help us to think more strategically about webs of strategies. It is a discussion of meta-strategy – strategies about how to pluralize strategies in the following ways:

- how to integrate punishment and persuasion, sanctions and supports, state regulation, self-regulation, co-regulation (Chapters 8, 9);
• how to regulate abuses in ways that strengthen innovation rather than weaken it (Chapter 8);
• how to sequence strategies; how to think in time about synergies among controls in order to produce a dynamic meta-strategy (Chapter 8);
• integrating ethical theory (theories of rights, of what should be criminal, when it should be punished) with regulatory theory, the normative with the explanatory (Chapter 9);
• how to network control strategies between governmental and non-governmental actors; how cosmopolitan enforcement can network the global and the local (Chapters 10, 11);
• how to combine private and public enforcement and foster creative new hybridities between the two in a transparent way (Chapter 10);
• how to strategize in a manner that is responsive to the way the pharmaceutical industry and contemporary capitalism are changing (Chapters 7 and 11);
• how to strategize about realities of entrenched power that make reform to control abuses of power difficult; searching for a politics of hope that helps us to see and seize an unforeseeable future (Chapter 11).

The ten themes and patterns revealed in Parts I and II could be read as pointing to a false dawn in the mid-1980s when a more ethical, innovative and law-abiding industry seemed to be emerging. Today, that industry appears in light of our analysis to be in fact less ethical, less innovative and less law-abiding than was the case a generation ago. After the scandal of Stanley Adams' false imprisonment for blowing the whistle to the European Commission over the vitamin cartel (one result of which was that his wife committed suicide), we never would have believed that the type of cartel that he revealed, one of the worst in the history of antitrust law, would have continued to betray the interests of consumers through the 1980s and 1990s (Chapter 6). We never would have predicted that fraud in the safety testing of pharmaceuticals would become even more extensive and more brazen in recent decades (Chapter 1) as compared with the extraordinary frauds of the 1960s and 1970s as documented 30 years ago in *Corporate Crime in the Pharmaceutical Industry*.  

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Peter Gøtzsche’s *Deadly Medicines and Organized Crime: How Big Pharma has Corrupted Healthcare* was released as we were sending this book to press.³ It documents in a different and insightful way how fraud in testing drugs has worsened. We never would have expected that enforcement of the False Claims Act (Chapter 10) would reveal the extent that this kind of fraud has in recent decades attained, as has fraud relating to pricing. We would not have expected the counterfeiting problem to get as severely out of hand as is now the case (Chapter 5). We would not have expected, following the apparent ethical renewal of the 1980s, to be reading Ben Goldacre’s damning 2012 summary of current malpractice,⁴ reflecting as it does a series of systematic studies and reviews. These point clearly to the frightening level to which scientific fraud in this field has now risen. Goldacre found that industry-funded trials of pharmaceuticals (since the 1980s) are about four times as likely to report positive results as are independent studies. And Gøtzsche shows that not only has the proportion of trials that are conducted by independent researchers declined sharply, with the percentage of US biomedical research funded by industry rising from 32 per cent in 1980 to 62 per cent in 2000,⁵ but also that between 1998 and 2004 there was a doubling of the number of talks delivered at pharmaceutical science conferences by industry salespeople.⁶ Between 1998 and 2005, fatal adverse drug events in the United States increased 2.7 fold.⁷

Not all of the explosion of deaths from adverse drug events is attributable to fraud, but Goldacre, like Gøtzsche, documents a more devastating litany of specific frauds than did Braithwaite in 1984. Beyond outright falsification of data and suppression of studies pointing to dangerous effects of drugs (essentially a form of censorship, enforced by gagging clauses in contracts with researchers), Goldacre points to patterns of deceit that involve variously “testing your treatment in freakishly perfect ‘ideal’ patients”, testing one’s product “against rubbish”, wilfully running trials that are too short, stopping trials early when the results are on the up, terminating trials if results are down (and starting the trial again), producing trial reports that bundle outcomes in a misleading manner, and conducting trials that ignore drop-outs, harking back to the

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⁶ Ibid., p. 95.
⁷ Ibid., p. 115.
"reincarnated rats" revelations of the 1970s, where rats (and dogs and 
monkeys) that died after exposure to a drug were replaced with healthy 
animals.\(^8\)

This is why we were able to conclude in Part II that the sums of money 
changing hands in pharmaceutical industry frauds, bribes, counterfeiting 
and cartels around the world have increased dramatically in real terms 
since the 1980s. And this in turn is why Russell Mokhiber's \textit{Corporate 
Crime Reporter} concluded that 12 of the 20 top corporate criminals of 
the 2000s were pharmaceutical companies,\(^9\) up from 6 of the top 20 in 
the 1990s.\(^10\)

Not only is outright defiance of the law a large problem, so is what is 
sometimes called "gaming the law" to avoid its strictures. Profit shifting 
to avoid any tax liability in many of the countries in which the industry 
operates is a classic example of gaming the law. It is an instance of a 
problem that has worsened in recent decades to the point where many 
pharmaceutical companies in many countries, notwithstanding the accu­
mulation of large profits in those countries, pay no tax at all.\(^11\) A 
recurrent structural problem, as big pharma has become even bigger, has 
been a growing subservience to the marketing function of processes that 
were once driven by independent professionals. Research, philanthropy 
and self-regulatory activities are increasingly subservient to the influence 
of marketing managers. A normative perspective on how to view all of 
these patterns of abuse through a criminological lens is the main purpose 
of this chapter.

7.2 TEN LESSONS

To lay a foundation for the policy analysis in Part III of the book, we present here a simplified outline of ten lessons that have emerged repeatedly throughout the cases of misconduct considered in this book.

1. **Corporate crime kills and defrauds**  The boundary between criminal and civil misdeeds is often unclear. It varies between nations. It is often unethical rather than criminal conduct that costs lives. Even so, criminal conduct in the pharmaceutical industry is surprisingly widespread as a cause of all of the kinds of suffering discussed in Parts I and II. This is why the theme of this chapter is a criminological perspective. Russell Mokhiber, editor of the Corporate Crime Reporter, has documented in the Reporter not only the fact that corporate crimes against health and safety kill many times more citizens than do individual homicides, but that a vastly higher multiple applies when one compares the figures with those on property crime: “The FBI estimates ... that burglary and robbery - street crime - costs the nation $3.8 billion a year ... Health care fraud alone costs Americans $100 billion to $400 billion a year.”

2. **It is Getting Worse** While we do not conclude that John Braithwaite was wrong to find in his publications of the 1980s and early 1990s that the conduct of the pharmaceutical industry was becoming more ethical and more law-abiding during the 1980s, we do conclude here that this is no longer true. Corporate crime in the pharmaceutical industry appears to be on the rise.

3. **But the industry has ethical dissenters**  Starting half a century ago when Graham Dukes had his brush with the thalidomide disaster (Part I), we conclude that at all times, and even within the worst companies in the industry, there are ethical executives struggling to respect medical values. These include values about helping patients, maintaining the rule of law and showing respect for human rights.

4. **Insider knowledge holds one key** Good people in the industry frequently find themselves on a slippery slope with their career if they allow ethical values to compromise the ruthless drive for profits that defines the character of so much of the senior leadership of the industry. Good people are often afraid to speak out. Consequently a challenge of regulatory enforcement is getting inside

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knowledge of the abuse of power. This is part of the context for the priority we give to a more radical approach to supporting whistleblowers through expanding the reach of *qui tam* (Chapter 9), giving whistleblowers a share of corporate penalties.

5. **Scapegoating corrodes enforcement** Scapegoating is widespread. The most ethical people in the industry, and particularly whistleblowers, are among those most likely to be designated as scapegoats. CEOs are least likely. We saw this in John Braithwaite’s research three decades ago, with the discovery of “vice presidents responsible for going to jail” who were paid to be fall guys for the CEO if something went badly wrong. It follows that a simple-minded strategy of sending the bad guys to jail often results in the imprisonment of mere scapegoats.

6. **Complexity fogs enforcement** The organizational, financial and technical complexity of transnational pharmaceutical production has assisted companies to become adept at creating smokescreens of diffused accountability. It is often difficult to determine who is responsible for what. This hamstrings law enforcement. It also institutionalizes a disconnect between decision makers and the consequences of their decisions. This inhibits individual awareness and responsibility for impacts on society.

7. **A bedrock of professional consensus on standards renders networked regulatory governance feasible** In most domains of pharmaceutical regulation and self-regulation, the principles of good practice are well settled and subject to quite a high degree of consensus. Professionals do argue about specific rules and the tolerance levels associated with them. Yet regulatory professionals tend to agree most of the time about specific major decisions to approve and withdraw new products, when to recall a contaminated product or to change the list of indications for which a medicine is approved. This is why the regulatory agencies around the world mostly make the same decisions. It is also why progress with global harmonization of regulation has been considerable. Finally, this is why networked regulatory governance in developing countries can succeed in harnessing multiple sources of regulatory power, where each network partner agrees on the need for more effective regulation but lacks the clout to effect change on its own. Shareholders, regulatory and self-regulatory officers, health professions, trade unions on occupational health and safety, environmental NGOs, health NGOs, the media, all count among the diverse players that we have discussed. They all play a role in weaving weak individual threads of social control into a more resilient fabric.
8. **Gaming the law is problem**  Gaming of the regulatory rules in order to secure financial advantage is also widespread. The gaming mentality has undermined innovation and reduced compliance with the spirit of the law. Innovation fell off a cliff in the late 1980s and early 1990s.\(^{13}\) Evergreening (me-again) and me-too patents have replaced the substance with the appearance of innovation (Chapter 6). Pharmaceutical industry leaders have been shown to game competition law, patent law, tax law, and to exploit the failure of some developing countries to keep their drug safety laws up to date by conducting reckless drug testing programmes there. The industry has also been a leader in exploiting the failure of some countries to extend the protections of regulatory laws to prisoners and other vulnerable populations. It has also been much more sophisticated and ruthless than other sectors of business in the art of manipulation (Chapter 4) and in bribing state officials to corrupt the regulatory process.\(^{14}\) In recent years, as we saw in Chapter 5, some of the largest jurisdictions in the world – such as China and the European Union – have seen the heads of their pharmaceuticals’ regulatory authorities convicted of corruption. The final result of this gaming mentality is a pharmaceutical industry that pays little in the way of taxes to cover the damage it does, that has put good medicines increasingly beyond the reach of the poorest and sickest citizens even in the richest countries, and that afflicts consumers with greater volumes of ineffective or dangerous medicines than was once the case. The upshot is undermedication of the poor and overmedication of the rich, a phenomenon that runs parallel to nutrition, with hunger besieging the poorest citizens of the planet while obesity afflicts the richest. The steep growth of counterfeiting has modified this equation somewhat, as growing numbers of poor consumers are exposed to fake drugs that endanger their lives.

9. **Philanthropy is making a difference**  In reaction, there has been an inspiring philanthropic movement to make valuable medicines more readily available to the millions dying needlessly each year, particularly in Africa and particularly from HIV-AIDS. This has been business-led. Some pharmaceutical industry leaders have made

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\(^{14}\) Braithwaite, *Corporate Crime in the Pharmaceutical Industry*, op. cit., chapter 2, showed 19 of the 20 largest American pharmaceutical companies to have engaged in serious bribery and the twentieth to have engaged in more minor questionable payments to officials.
magnificent contributions to this reform project, others have gamed it (Chapter 6), though the most important contributors have been leaders from outside the pharmaceutical industry such as Bill Gates and Warren Buffet.

10. **Profits plunge as innovation hits crisis** The pharmaceutical industry was by far the most profitable business sector of the second half of the twentieth century for two main reasons. First, it rode the wave of the golden age of the biological sciences in the world’s great universities. The pharmaceutical industry likes to tout its accomplishments in innovation; our question is why these have not been stronger and more sustained when the industry was riding such a wave. Second, pharmaceutical companies established transnational coherence in their business strategies earlier than did other capitalist enterprises and cleverly manipulated those states which were slow to see the imperative for international regulatory collaboration (see Chapter 4).

7.3 **TOWARDS A CRIMINOLOGY OF CRIME IN THE SUITES**

Edwin Sutherland’s *White-Collar Crime*¹⁵ inspired a rich tradition of research into corporate crime.¹⁶ It showed the cost of crime in the suites

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A criminological perspective on a worsening crisis

to be much higher than that of crime in the streets. That tradition views as criminal some things that are normally presented to consumers as accidents. One influential book on corporate crime, by David Friedrichs, points to recent forensic studies suggesting that a cause of the sinking of the *Titanic* in 1912 may have been cost cutting by a shipping company that authorized the installation of substandard rivets in the construction of the ship.\(^{17}\) Of course, seeing those who perished on the *Titanic* as victims of a corporate crime is just one lens through which we can view their suffering. Likewise Friedrichs finds corporate crime a useful lens (though not the only one) through which we can understand the global financial crisis of 2008. In the present book we also find the corporate crime lens useful for comprehending loss of life among pharmaceutical consumers. But we seek a more stereoscopic view of the dilemmas of pharmaceutical crises by simultaneously viewing the problem through many other lenses.

It is hard to quantify the impact of the misconduct discussed in this book. In most nations, as we have noted above, it almost certainly costs many more lives than individual homicide.\(^ {18}\) We will see, however, that interpreting these data is difficult. In poor countries and among the poor of rich countries, monopolistic practices that render drugs unaffordable take a huge toll on sick lives. We do not know the number of people who would live rather than die each year if they could afford relevant drugs, but we can be sure that it runs into the millions. It is claimed, for example, that the many hundreds of millions of dollars that have been leveraged from initial funding by the Gates Foundation to the Global Alliance for Vaccines and Immunisation and the Global Fund to fight HIV/AIDS, Tuberculosis and Malaria have prevented five million deaths and vaccinated more than 250 million children at risk in poor countries.\(^ {19}\)

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\(^{18}\) Police homicide statistics of course do not count corporate homicides, indeed do not think of this as a homicide problem that is the responsibility of the police to count.

We can get an inkling of the magnitude of the toll from research on hospital admissions. This suggests a death toll from “adverse events” (defined as incidents in which harm resulted from a person receiving health care) that is many times the homicide rate—even among the general populations of the richest of nations. In the United States, the Institute of Medicine found 44,000 to 98,000 deaths and a million injuries a year from adverse events in healthcare institutions. Comparable British and Australian studies paint at least as grim a picture. Australian research found not only comparable numbers of adverse events in hospitals, but that 16.6 per cent of hospital admissions were a result of adverse events. A total of 18,000 deaths each year from medical errors and 50,000 cases of permanent disability from the same cause were estimated from that analysis of medical records. Homicides in Australia (murder and manslaughter combined) have been taking fewer than 300 lives each year in recent years, down from 400 in earlier periods of its history. Homicides are less likely to be undercounted than are deaths from medical errors; a body found with a knife protruding will be counted as a murder; by contrast a fatality due to misuse of pharmaceuticals may well be counted as a death from the disease that the drug was intended to treat. On the other hand, most adverse events in health care are not caused by use and misuse of drugs and most misuse of drugs is not due to pharmaceutical industry misconduct. The Australian Institute of Health and Welfare found that for more than a quarter of medical errors, drugs were at least one of the causes. Other estimates are lower,
between 10 and 20 per cent.\textsuperscript{25} If we take the lowest estimate of 10 per cent, recorded misuse of drugs still causes more than six times as many deaths in Australia each year than are attributable to recorded murder and manslaughter combined. The European Commission estimates that adverse reactions to drugs kills nearly 200,000 Europeans each year,\textsuperscript{26} more than eight times its homicides (23,000) in 2010.\textsuperscript{27} There are multiple interpretive challenges with these comparisons, particularly with ascertaining the contribution of false advertising, fraudulent science, bribery of health professionals and other offences we have discussed. And these numbers are undoubtedly small compared with the millions killed by undermedication of the poor as a result of monopoly pricing, or compared with dangerous medication caused by counterfeiting in poor countries.

One estimate of the number killed by the blatant fraud of pharmaceutical counterfeiting for malaria and tuberculosis, much of it by Chinese or other Asian producers, is 700,000 a year.\textsuperscript{28} The scale of the counterfeiting problem seems to have at least doubled so far this century, with 30–50 per cent of pharmaceuticals sold now being fake in the developing countries with the worst problem.\textsuperscript{29} 700,000 is more than all the people killed across the globe by homicide, terrorism and warfare combined for any year of this century so far.\textsuperscript{30}

\textsuperscript{25} Ibid., p. 3.
\textsuperscript{26} Archibald K, R Coleman and C Foster (2011), ‘Open letter to UK Prime Minister David Cameron and Health Secretary Andrew Lansley on safety of medicines’, \textit{Lancet}, 377, 1915.
\textsuperscript{29} Ibid., p. 8.
Single medicines that have been misleadingly marketed may also have been responsible in recent years for killing a six-figure quantum of patients. Gøtzsche estimated that the US company Merck was responsible for 120,000 deaths worldwide by 2004 through thrombosis caused by Vioxx, which was misleadingly evaluated. Merck pleaded guilty in 2012 to criminal charges for its promotion and marketing.31 By 2007 Gøtzsche estimated that Lilly’s top seller Zyprexa had killed 200,000 worldwide, partly on the back of illegal marketing for numerous off-label uses, including Alzheimer’s, depression and dementia, for which it forfeited $1.4 billion in civil and criminal penalties.32 These deaths caused by US companies compare with 14,612 murders and manslaughters known to the FBI in the United States during 2011.33

Blatant fraud, while it is a substantial part of the problem, bears less of the responsibility for these deaths than gaming the law. While studies that suggested that a product like Lilly’s Zyprexa was dangerous were suppressed, its Cochrane review from 2005 reported that one encouraging study was published 142 times in papers and conference abstracts!34

In spite of the difficulties with making some of these comparisons, the numbers are sufficient to suggest that there is something awry in the discipline of criminology. So many criminologists study individual homicide, while so few have chosen to view the topic of this book as a matter meriting their attention.

7.4 THINKING ABOUT THE STRENGTHS AND THE WEAKNESSES OF CRIMINAL LAW

This book argues that seeing injuries from misuse of medicines as a crime problem is a useful lens. While we argue against an approach to prevention based on locking up hundreds of executives from the pharmaceutical industry, we will argue that the criminal law can help to control deadly corporate cultures because of its symbolic power. This power has been greatly under-used against the pharmaceutical industry. In addition

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32 Ibid., pp. 230–32.
34 Gøtzsche, Deadly Medicines and Organized Crime, op. cit., p. 231.
we will argue in Part III that the greatest potential of criminal enforce­ment for cleaning up the pharmaceutical industry lies not in increasing punishment, but in increasing detection. We argue for a pyramid of regulatory strategies where criminal punishment has an important role near the peak of the pyramid. It is a role that motivates detection and prevention by adopting less punitive strategies at the base of an enforce­ment pyramid.

Arguing in this distinctive way for the value of a criminological lens on the worsening crisis of the pharmaceutical industry, we do not mean to assert that it is the main lens. In Chapter 11 we commend the lens of looking for a new kind of capitalism that will nurture new business models, fostering innovation and ethics; we argue too for a new kind of international drug diplomacy that can inspire institutional change. These are even more important lenses than the criminological one, though, as we shall see, they complement it.

In this criminological and regulatory policy sense, the present book is very different from the splendid blossoming of books we have seen recently from distinguished authors such as Ben Goldacre\(^\text{35}\) and Peter Gøtzsche.\(^\text{36}\) At times, the language of Gøtzsche’s book is less moderate than we would use, but there can be little doubt of the sharpness of the methodological insights of the distinguished co-founder of the Cochrane collaboration who has himself published more than 50 papers in “the big five” (BMJ, Lancet, JAMA, Annals of Internal Medicine and New England Journal of Medicine). This is why forewords to his book were written by a former editor-in-chief of the British Medical Journal and a deputy editor of the Journal of the American Medical Association, Richard Smith and Drummond Rennie. In recent years we have also seen devastatingly critical books about the declining ethics and performance of the pharmaceutical industry by two previous editors of the New England Journal of Medicine, Marcia Angell\(^\text{37}\) and Jerome Kassirer\(^\text{38}\) and an editor of the British Medical Journal, Richard Smith.\(^\text{39}\)

\(^{35}\) Goldacre, Bad Pharma, op. cit.
\(^{36}\) Gøtzsche, Deadly Medicines and Organized Crime, op. cit.
have concentrated on particular areas of medicine; both Robert Whitaker\textsuperscript{40} and David Healy\textsuperscript{41} portray the disastrous influence of the industry in the field of mental health, while in no sense ignoring the simultaneous failure of the health professions. These books by scholars of extraordinary experience of the realities all converge on a diagnosis of catastrophic industry and regulatory failure. In the remainder of this book, we show how the distinctive way we have narrated that crisis in Parts I and II opens our eyes to fresh regulatory insight for a transformative way ahead.


8. Positive regulation: The complementary role of supports and sanctions

8.1 THE CHAPTER IN BRIEF

We begin this chapter by presenting the case for an integrated approach to countering all the forms of misconduct discussed in Part II. This will involve creating a hierarchy of strategies for building on the strengths of the pharmaceutical industry, while adopting in parallel with this a mix of strategies for enforcement. Within the hierarchy of strategies for building strengths we find that patents dominate thinking far more than evidence as to their effectiveness warrants. It may well be that patent terms need to be reduced, options for compulsory licences on patented drugs extended and complementary reward systems for innovation strengthened if patents are to contribute to a reversal of the steep decline in pharmaceutical innovation that has been seen over the past 25 years. Patents are simultaneously a strength and a weakness of the innovation system, encouraging innovation by some but preventing innovation by others. Open-source biotechnology to reinvigorate pharmaceutical innovation, complementing the patent model of innovation, is one option. Society has failed to adopt an evidence-based approach to determine how one might craft patent law so that it does less harm and more good than is currently the case. If we over-use overly long patents, their benefits in terms of innovation will be outweighed by the cost to society resulting from prolonged maintenance of monopolies.

We are troubled that the pharmaceutical industry has allowed investment in real research and development to fall. We are troubled that "the return on investment for legal tactics is a lot higher than the return on investment for R&D".\(^1\) We find the political lobbying, campaign contributions and bribery undertaken by the pharmaceutical industry in order to protect inefficient

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forms of monopoly power and to insulate firms from criminal enforcement (Chapters 4, 5) to comprise one of the major dangers confronting humankind today. Criminal enforcement is so uncommon and many regulators are so ensnared by the industry that radical remedies are called for to cure an ailing, monopoly-ridden industry.

Chapter 10 considers the possibility of expanding the scope of the one major step forward in enforcement against drug company abuses adopted in recent decades, namely the 1986 amendments to the False Claims Act in the United States. This law reduces reliance on regulators who may be captured or corrupted by partially privatizing enforcement. It opens up a potential for more creatively productive synergies between private and public enforcement. More creative interplay between private and public enforcement is conceived as particularly important to the networked regulation of drug safety in developing economies. We shall go on to consider the equity fine as a sentencing reform that might further add to private-public enforcement synergies. Finally, in Chapter 10 we shall consider the potential for providing more open accountability for the pharmaceutical industry via the internet. One conclusion of that chapter will be that corporate crime in the pharmaceutical industry reveals the obsolescence of mainstream jurisprudence in criminal law. We shall also argue that competitive audit of industry compliance reported on the internet can help, especially in developing countries.

8.2 BUILDING ON STRENGTHS

Just as the first half of the twentieth century was a period of unprecedented progress in physics and mechanical engineering, the second half of the twentieth century was one of stunning surges in biology and medicine. Biology has advanced in the rigour, quantity and integrity of research and in theoretical breakthroughs. As a result, biologists of all kinds, including pharmacologists and physicians, have gained a deeper sense of professional pride in developing evidence-based insight. It is therefore not surprising that pharmaceutical innovation boomed for four decades after World War II. The surprising thing is that innovation nose-dived after the mid-1980s.²

There are those in the industry who blame this collapse of innovation on regulation. Yet internationally the strongest growth seen in drug regulation occurred between the late 1950s and the early 1980s, with the

thalidomide disaster prompting the sharpest surge in 1960–63. Then, after the Reagan and Thatcher administrations got into their stride, there appeared to be an increase in the numbers of pro-industry drug regulators. From the 1980s onwards, the rate of growth of regulation fell in many countries. Deregulatory initiatives were put in place. The United States and other countries considerably reduced the "drug lag", i.e. the time elapsing between the invention of a drug and its approval for marketing. One of the most destructive regulatory changes of the late twentieth century was the movement of most countries away from funding drug evaluation from the public purse to funding by fees paid by the drug companies. This motivated national regulators such as the US FDA to compete for drug registration income with quicker and more cursory drug evaluation procedures. Unsurprisingly, the streamlined FDA became the best competitor in this market for regulatory services, with the percentage of new drugs introduced to the world market first approved at the FDA increasing from 4 per cent in 1988 to 66 per cent by 1998. One of the ways in which the FDA won this race was by halving the proportion of new drug applications that it rejected during the 1990s.

The biggest changes in the Reagan years, however, had been the passage of a variety of laws that extended monopoly rights for brand-name drugs. These increased the incentives for patented products to a point where, in 2002, after more than a decade and a half of decline in innovation, the top ten drug companies in the Fortune 500 together made a profit exceeding that earned by the other 490 companies on the list! After 2002, drug companies, following half a century during which they had been the most profitable sector in international business, began to experience declining (though still high) profits as their failure to sustain innovation finally caught up with them. The industry proved bereft of new breakthroughs to replace their expiring monopolies. Monopoly seemed to have the effect of pampering them into sloth and gameplaying rather than stimulating them to probe for new discoveries.

In the 1990s and 2000s, the International Conference on Harmonization began to make some progress in enabling nations to recognize drug evaluation and other regulatory work undertaken on foreign shores. Burden sharing through various kinds of international collaboration in

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4 Ibid., p. 115.
6 Ibid., p. 11.
matters of regulation and research is an emergent strength. There have also been important national initiatives in this field. One was the US Food and Drug Administration’s “Critical Path Initiative”, introduced in 2003 to promote collaboration between industry, government and academia in order to expand the “tool kit” for translating basic research discoveries into safe and effective drugs, for example through developing techniques for the early detection of safety problems.\textsuperscript{7}

Another international strength has been that orphan drugs, the main market for which is in developing countries, today receive more backing than in past decades. Multinational companies, wealthy states, the World Health Organization and philanthropies such as the Gates Foundation have all played important roles in bringing about that improvement. Non-profit bodies such as the “Drugs for Neglected Diseases Initiative” in Strasbourg and “One World Health” in San Francisco also came into being.

8.3 TWO PYRAMIDS: SUPPORTS AND SANCTIONS

Stronger science, stronger professionalism and stronger international collaboration are splendid strengths on which to ensure that drugs contribute more to the life of humankind. While we have seen that there are myriad problems in the pharmaceutical industry, while regulators must “pick important problems and fix them”,\textsuperscript{8} they must also “pick strengths and expand them”.\textsuperscript{9} Figure 8.1 presents the concept of an integrated pharmaceuticals policy that does both by integrating a strengths-based pyramid (pyramid of supports) and a regulatory pyramid (pyramid of sanctions). Our preference is to ensure movement up the pyramid of supports wherever we can. We can distinguish the design principles of a regulatory enforcement pyramid and a strengths-based pyramid in the following way:


Table 8.1  Comparing design principles for regulatory and strengths-based pyramids

<table>
<thead>
<tr>
<th>Regulatory pyramid</th>
<th>Strengths-based pyramid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk assessment</td>
<td>Assessment of opportunities</td>
</tr>
<tr>
<td>Fix problems</td>
<td>Innovate to circumvent or avoid creating problems</td>
</tr>
<tr>
<td>Progress by narrowing the scope of problems</td>
<td>Progress by expanding the scope of strengths</td>
</tr>
<tr>
<td>Prompt response before a problem grows</td>
<td>Wait patiently to support strengths that bubble up from below</td>
</tr>
<tr>
<td>Pushing standards above a floor</td>
<td>Pulling standards through a ceiling</td>
</tr>
</tbody>
</table>

Figure 8.1  A pharmaceuticals pyramid of sanctions and a pyramid of supports

In other words we can reduce risks to public health by targeting them through a regulatory pyramid. Or we can expand strengths until they grow to conquer risks. To put it another way: we can prevent a child from falling by strapping it into a pram (containing risk) or we can teach it to walk (expanding strengths).
Universities and professional colleges and research funding agencies have vital roles to play in spotting fertile new developments and integrating them into educational and research priorities at the base of a pyramid of supports. The next rung up the pyramid of supports reflects the important research finding that, when government inspectors visit a firm, one of the most important things they can do to improve compliance between this inspection and the next is deadly simple. It is just to notice the things that have improved and to heap praise on the professionals responsible for that improvement.\textsuperscript{10} So obvious a regulatory strategy: an inspection policy empirically validated as extremely cheap and effective, yet so neglected.

When a pharmaceutical research or production organization has shown some exceptional strength, governments can award it grants or prizes to further build that strength. Prizes can be awarded to firms that show extraordinary improvement and innovation in Good Manufacturing Practices (GMPs), Good Laboratory Practices (GLPs), ethical marketing practices, and so on. An important proposal is Jamie Love and Tim Hubbard’s idea of prizes to stimulate R&D for new medicines.\textsuperscript{11} The beauty of their idea is that it offers a complete and radical alternative to patents as a means of rewarding therapeutic breakthroughs. It also opens a gradualist path to change. A gradualist path in one country would be to reduce patent terms and put all the savings that accrue to the government health budget into the prize fund, while urging private hospitals and other large private purchasers to do likewise. Naturally, we should not underestimate how hard these things would be to achieve. Public health leadership to revise the TRIPS agreement at the World Trade Organization would be needed. That leadership would need to be as bold as the US corporate leadership that created TRIPS.\textsuperscript{12}


Thomas Pogge has developed a reward strategy that is TRIPS-consistent for getting medicines to the poor. This involves governments underwriting a global Health Impact Fund. Such a fund would reward the patentee of any new medicine with annual payments proportional to the drug’s demonstrated global health impact. Registering with the fund would be voluntary for the owner of a patent. The fund would then allow a variety of hybrid paths to product marketing. One would be for the firm to waive permanently its patent monopoly in return for the reward payment. Generic competitors would then be allowed to drive the price down to a level approaching the long-run marginal cost of production. This would also largely remove the lure of counterfeiting. Taking the Health Impact Fund reward to surrender patents would become the rational track for cures for tropical diseases with miniscule first world markets. Pogge argues that for products targeting hair loss or acne, in contrast, where developing country markets are tiny and Health Impact Fund rewards similarly small, firms would do best to recover the costs of their innovation and make profits by using patent monopolies in the traditional manner. Another Pogge option that could be slotted into a pyramid of supports is that, in return for a certain level of reward payment, the patent holder would be required during a negotiated period to sell the medicine at an agreed low price; when that period expired, the firm would be required to offer zero-priced licences to others to manufacture the product.

There can be many gradations in how to move up a pyramid of supports by awarding bigger and bigger prizes for more and more fundamental innovations. Industry-university research clusters that are pioneering more valuable inventions than other clusters could receive government funding support for biotechnology exchange clearinghouses to make it easier for new players to access knowhow and join the cluster. Foreign aid should be extended to scientists in developing countries to enable the transfer of technology that would encourage them to steer the course of invention towards the diseases most prevalent in those countries. Peter Drahos’s idea of an indigenous knowledge clearinghouse is

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15 Drahos P (2004a), ‘Towards an international framework for the protection of traditional group knowledge and practice’, Draft paper prepared for the
also relevant here. It could add extra value for UNESCO each year to lionize a person or organization for having made a special lifetime contribution to facilitating a flow of benefits from indigenous knowledge to indigenous peoples, while making areas of indigenous knowledge part of the common heritage of humanity. This could reinforce biodiversity with cultural diversity.

In medicine, the Nobel Prize is the ultimate accolade, and one that inevitably floods winners and their laboratories with reputational capital and streams of research support. We have therefore illustrated our pyramid of supports for continuous improvement in ethical innovation with a Nobel Prize at the peak. Being a design that is responsive to actors and circumstances, there is no single or correct set of ideas for what is included in the layers of a pyramid. Different challenges of pharmaceutical regulation (GMPs versus GLPs) will require various pyramids. Different countries at different points in history will design with their stakeholders of that time and place different layers of escalation. That is the essence of responsiveness.

8.4 PATENT REFORM

The patent system has been an important means of ensuring reward for innovation, and one that continues to have a strategic place in the higher reaches of a pyramid of supports for pharmaceutical excellence. Yet today, as we saw in Chapters 4 and 6, that is a contested place. The contest has arisen because walls of patents are increasingly erected to thwart innovation by others, while at the same time rewarding the firm which has been granted the patent.16 Specific patenting techniques for


16 This is not to say that the pharmaceutical industry was the first to invent walls of patents to prevent competitive innovation on patents that then tragically lie fallow. Thomas Edison took the first steps toward this strategy. Older industrial firms like IBM, which saw the virtues of R&D, perfected it. The strategy of erecting a wall of patents to keep others out, as opposed to claiming patents in order to use them, may be spreading to biotechnology. In the 1990s, 90 per cent of biotechnology patents were never used, and all the empirical studies devoted to the matter find that the intellectual commons is threatened by growing anticommons risks in the biological sciences (Walsh J, A Arora and WM Cohen (2003), ‘Working through the patent problem’, Science, 299, 1021. Nicol D and J Neilsen (2003), ‘Patents and medical biotechnology: an empirical analysis of
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blocking innovation include “clustering” (patenting around the company’s own patents), “bracketing” (patenting around a competitor’s patents), “blitzkrieg” (patenting a great number of similar or related molecular entities), “blanketing” (mining every step in a manufacturing process with patents claiming minor modifications), “flooding” (taking out many patents for minor variations on an innovation developed by another company), “fencing” (blocking certain R&D directions with a series of patents) and “surrounding” (enclosing a key patent in a ring of minor patents that collectively block its effective commercial use). The system increasingly diverts research funds from inventing the new to evergreening the old (Chapter 6). As effective patent monopolies have become longer, the pharmaceutical industry has become a monopolists’ club. In the course of the second half of the twentieth century, the industry progressively became fat and lazy. As a result of a business model based on clinging to patent-based monopolies, the industry then became much less profitable during the next decade compared with the extraordinary profitability it enjoyed until 2002. It invested an ever greater proportion of its funds in marketing campaigns intended to extend the effective market life of money-spinners once their patents expired, into political lobbying and corruption to quicken marketing approval and lengthen patent terms, into lobbying for TRIPS and then for bilateral trade agreements to expand patent monopolies and into evergreening research instead of undertaking truly adventurous innovation.

The problem was eloquently portrayed by Peter Ringrose, chief scientific officer of one of the pharmaceutical giants, Bristol-Myers Squibb, when he told the New York Times that there were “more than 50 proteins possibly involved in cancer that the company was not working on because the patent holders either would not allow it or were demanding unreasonable royalties”.

Italy is an interesting case study of how critical patent monopolies are to innovation. Even though Venice was the place where modern patents

issues facing the Australian industry’, Centre for Law and Genetics, Hobart, Occasional Paper No. 6).


of inventions and patent office administration (which became the model for the US Patent Office)\textsuperscript{19} were invented, Italy was in 1978 the last of the western economies to extend patent protection to pharmaceutical products. Boldrin and Levine\textsuperscript{20} show that the rate of discovery of new compounds in Italy did not increase after pharmaceutical product patents were enforced; indeed it fell somewhat, in terms of both the absolute numbers of discoveries per year and in the proportion of new compounds introduced globally that had been discovered in Italy. The innovation that was happening in Italy up to 1978 involved domestic Italian generic manufacturers actually discovering improved compounds in the process of copying or reverse engineering foreign patents. Italy had some good universities; genuine pharmaceutical innovation depends much more on the quality of the research supported in a nation’s universities than in big pharma’s laboratories.\textsuperscript{21}

One of the things that a pyramid of policy supports might encourage is the development of open-source biotechnology as an alternative business model to one based on patent monopolies.\textsuperscript{22} In information technology, open source has provided an alternative intellectual property model competing in parallel with the patent/copyright model lobbied for by the dominant IT firm of the twentieth century, IBM. Alongside big pharma, IBM was also the pre-eminent lobbying partner for TRIPS in the World Trade Organization. However, IBM did not retain its dominance of IT to the end of the twentieth century in the way that big pharma continued to dominate its own sector. IT has become a progressively more innovative sector, while pharmaceutical innovation has declined. The existence of a radical alternative innovation model in open source is one reason why IT has been better at renewing itself, to the point where once dominant firms such as IBM, Sun Microsystems and even Microsoft have found that the surest path to survival has been to embrace open source in addition to competing with it.


\textsuperscript{22} Hope J (2007), \textit{Biobazaar: The Open Source Revolution and Biotechnology}, Cambridge, MA, USA: Harvard University Press. For one attempt at crafting pyramids of supports and sanctions for biotechnology, see: Hope et al., ‘Regulatory capitalism, business models and the knowledge economy’, op. cit., chapter 5.
Open source can work under a wide plurality of business models in biotechnology. The basic model is that a firm makes a discovery, patents it, then sells licences to anyone who wants to obtain them on condition that they will on-licence any further improvements that they make to the initial innovation. Everyone is rewarded for making further innovations because they can on-sell them; everyone benefits from existing innovations. As in open-source information technology, communities of innovation evolve that create wealth together on the back of the synergies among their various innovations.

It is hard to say whether open-source biotechnology can ever make anything like the contribution to drug innovation that open source has made to IT. Much more capital is needed to start up as a biotechnology innovator than as an IT inventor. On the other hand, the public funding available to universities and other laboratories for biotechnology innovation is vastly greater than in the case of IT. The degree to which open source can flourish in biotechnology is a question that can only be answered through an evidence-based approach. And of course it is a matter of being as innovative in putting together business models as the pharmaceutical industry has been innovative in building molecules. The research of our colleagues, Janet Hope and Di Nicol, on options for open-source business models in biotechnology is therefore of critical importance. The government of India has taken an important lead in funding and encouraging universities to support an Open-source Drug Discovery project and portal (http://www.osdd.net/) focused on generic drug discovery to combat tuberculosis. The funding is modest; a lot of funding over a long period will be necessary to develop new drugs that can conquer multiple drug-resistant tuberculosis.

Another of our collaborators, Peter Drahos, works on the reform of patent office administration, rendering it much more difficult to erect the walls of patents that so frustrated Bristol-Myers Squibb’s Richard Ringrose. Frederick Abbott and Graham Dukes have proposed that patent administration needs to “raise the bar on the inventive step” so that only those new drugs that provide a mechanism for targeting a disease in a substantially different way from prior drugs will be eligible for patenting, and “demonstrations of efficacy” will be an essential condition.

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23 See the references at notes 13 and 17.
for obtaining the grant of a patent. Another colleague, Luigi Palombi, has worked on alternative legal reforms to the patent system. One of his specific concerns is the danger resulting from extension of the patent system to embrace gene technology.

Peter Drahos contends that if such ideas are to be given breathing space despite the suffocating sway of big pharma over the world’s patent offices, it will be necessary to establish a counter-network of outsiders: “The only way to counter the power of one network is with another network”. Not all the parties in the proposed Drahos network would be outside government: working in the network alongside academics and health non-governmental organizations (NGOs), indigenous and farming groups, one would find officials of government departments of health and of the agencies dealing with the environment and with competition. He envisages the network setting up an independent committee of experts that would include Nobel laureates to target a key area of patenting each year. At the international level, the committee would call to account patents in that area by submitting to parliamentary enquiries and the media available evidence as to whether those patents were increasing or reducing innovation. Drahos’s network could also take on the critical challenge of rendering innovation in patents more meaningfully transparent so that existing patents form a stronger foundation for further innovation. Health Departments or the WHO could learn from the efforts of the US Department of Agriculture in compensating for the failure of patent offices to make patents in agricultural biotechnology transparent by undertaking that task itself.

More mundanely, research is needed on the optimal duration of patents that will jointly maximize rewards for inventors and minimize denial of access by inventors to the foundations for further invention. Research is needed on how patent terms might be reduced to that optimum through the provision of other rewards such as generously funded prizes in a pyramid of supports. We should not be ideological about such questions; big pharma has been all too doctrinaire in harping on the notion that greater use of patent-based monopoly rights will necessarily foster more

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26 Palombi, Gene Cartels: Biotech Patents in the Age of Free Trade, op. cit.
28 Ibid., p. 300.
innovation. In such matters, one’s approach must be based on firm evidence and not on a creed.

An experimental approach to some aspects of the law is also called for. One such study could well assess the impact of allowing public interest suits seeking to impose an obligation on patent offices to grant licences where courts consider that this would be beneficial to the public’s health. Examination of the potential benefits conferred by permitting such suits would involve setting the advantages of greater incentives to primary inventors against the benefits of allowing inventors from other firms to build on the primary invention (and to sell life-saving drugs to patients at more competitive prices). Newly industrializing countries are probably the best places for such legal experiments to be conducted with financial and scientific support from western foundations and universities and from the World Health Organization (see Chapter 4). In other areas, making regulatory agencies accountable to public interest groups and the courts has allowed independent agencies to do a commendable job of implementing tests that require them to balance the public benefits of competition against different kinds of public benefits and costs of monopoly. The idea is therefore not radical; one merely applies to the pharmaceuticals sector lessons learnt from experience in other areas.

Like many national competition regulators, the Australian Competition and Consumer Commission authorizes professional associations, such as those representing lawyers, doctors or architects, to enjoy professional monopolies with regard to certain activities from which alternative practitioners are excluded. 29 This is just one of many areas in which Australian law empowers the Commission to make judgements as to whether the benefits of monopoly exceed the benefits of competition, or vice versa. The regulator issues a draft decision on how it proposes, in a given area, to balance the public interest against that accruing from a policy of free competition. All the stakeholders are then invited to challenge the draft at a pre-decision conference. Carpenters and consumer groups might for example attend to challenge monopoly rights that they believe are too wide in allowing only trained architects to design buildings. They might contest this monopoly if they believe that it goes too far in preventing contract builders from erecting cheap homes for the poor. During his decade as a Commissioner, John Braithwaite chaired a hearing on a draft authorization regarding opiates that was challenged by big pharma. Firms such as Glaxo believed that the Commission’s draft

authorization gave the Tasmanian Poppy Growers Association too exclusive a monopoly over the legal production of opiates. The poppy growers and the police argued for tight regulation of poppy production in the hands of a modest number of licensed growers in the public interest of preventing diversion of opiates to organized criminals. Big pharma wanted to see more competition between rival growers in terms of pricing. In such matters it can be difficult to arrive at a fair and balanced assessment of the competing arguments. An assessment can however be carried out effectively in a deliberative circle where all the contesting voices are heard and considered, and where any element of corruption or commercial capture in judging the balance can be contested in the courts. With patents that are unusually critical to public health, there is a need for experimentation with different methodologies for patent offices and courts to hear challenges that propose modifications to patents or their licensing after balancing all the public interests at issue.

8.5 DESIGNING A RESPONSIVE REGULATORY PYRAMID FOR PHARMACEUTICALS

The idea of responsive regulation is that the community must be able to respond if firms fail to advance sufficiently, given the incentives provided by the pyramid of supports on the left side of Figure 8.1. This response involves progressively moving up the pyramid of sanctions on the right side of Figure 8.1, but only as far as necessary. It is preferable to solve problems at the base of the pyramid of sanctions by education, persuasion and negotiation. In the first instance, one appeals to the professionalism and ethics of those working in the company to voluntarily craft their own remedies to temper such corporate conduct as could present a threat to public health. For example, if regulatory audits of Good Manufacturing Practices (Chapter 2), of Good Laboratory Practices (Chapter 1), clinical trials (Chapter 1), marketing practices (Chapter 3), fraud and corruption compliance (Chapter 5) or antitrust compliance (Chapter 6) reveal a pattern of poor practice, the best remedy will generally be to invite the company to put in place a plan to eliminate the problem. If management does this promptly, then by the time the regulator presents the result of its audit on the internet, the regulator will also be able to praise the company for responding so positively to criticism.

Where the company responds optimally by devising new self-regulatory strategies that could underwrite continuous improvement in the industry as a whole, the regulator can heap praise upon the company
on the website. This is an important process with a firm basis in past experience: the history of business regulation across many sectors is that companies that lead industry compliance technologies up through new ceilings are often the companies that have suffered serious enforcement action for non-compliance. By giving the company time to respond or object to the audit report that will be lodged on the regulator’s website, time is also granted for the company to respond by setting its sails to become the industry leader in compliance innovation, moving the firm to the second rung of the pyramid of supports in Figure 8.1.

Of course, not all firms will be sufficiently responsible or nimble enough to snatch state support from the jaws of sanctions. The first step up the pyramid of sanctions is simply to lodge on the regulator’s website the adverse audit report, unqualified by any evidence of improvement. The response would not be limited to the website; the regulator will, in regular press releases pointing to new audit results, draw the attention of medical journalists, editors of health journals, professional associations and consumer associations to its findings. Where audit results are particularly unfavourable, the firm in question could, we suggest, expect a harvest of adverse publicity and loss of professional repute at the second rung of the regulatory pyramid. Sometimes it will successfully manage the impact of that publicity, sometimes not.

When evidence does not appear on the regulator’s website that the problem has been fixed, and that new mechanisms have been put in place to prevent recurrence, the regulatory body can itself also expect to be faced with adverse publicity for failing to take further action. It may then be forced to move further up its regulatory pyramid. Corporations are often impervious to naming and shaming. Where this is the case, firmer regulatory action may be called for. The idea of the pyramid reflects the assumption that at any level the regulatory response will sometimes prove inadequate. It seeks to compensate for the weaknesses of one enforcement strategy by resorting to the strengths provided by others. Most of the ideas in the pyramids discussed in this chapter are not new and have been tried and tested in the pharma sector (see Part II). Even so, we believe there is a need for a new redundancy in regulatory design that covers the weaknesses of each strategy in the contexts where they are found to fail.

Pyramids of sanctions with different content need to be designed for different kinds of regulatory challenges. If a misleading advertisement has been published, remedial advertisements of a certain size and content may be ordered in all the leading medical journals that point out precisely why the previous advertisement was misleading. If Good Laboratory Practices have not been followed, a firm could be required to
contract out to a reputable university research group a replication of all the suspect trials until such time as credible new internal compliance procedures for GLPs have been put in place at the company. If studies revealing the dangers of a drug have been suppressed, the company might be required to maintain a transparent public register of all the trials it initiates. If the audit has revealed a pattern of sloppiness involving GMP or occupational health and safety issues, a production line might be shut down until new controls have been implemented on that production line. If the firm has dragged its heels on implementing the necessary remedies, the regulator should have the power to impose civil penalties that accumulate as per diem fines. Imposition of fines that grow each day will mean that if a firm deals with the problem quickly, the fine will remain so modest as to not be worth appealing. The fine will become larger and positively painful if the firm over a longer period delays action or denies responsibility.

Even if the conduct involves a very serious crime, one would not advise hasty recourse to incarceration of the pharmaceutical industry’s corporate criminals. That is not to say this should never happen; it is merely to argue that knee-jerk maximal punitiveness is not the way to save most lives. One reason, already touched on above, is that, as we know from decades of experience with our colleagues in the pharmaceutical industry, the latter are adept at scapegoating (Section 7.2 above). Yet the more important finding of our enquiry is the creation of smokescreens of diffused accountability, whereby everyone has a credible reason for laying the blame on someone else, so that holding any particular individual accountable can be invidious. A smokescreen of diffused accountability can be blown away by regulators requiring compliance policies that nominate specific managers as responsible for signing for the fact that specific compliance obligations have been met. Once that is accomplished, however, the risk remains that a corrupt organizational culture will escape scrutiny as all blame (and not merely specified forms of blame) is shifted onto a nominated individual. Part of the idea of the regulatory pyramid is to both reduce the costs of regulation and increase its benefits by driving regulation down to the base of the pyramid. Indeed one of the ways to evaluate responsive regulation in a particular context is to measure how effective its introduction proves to be in reducing regulatory burdens by getting problems fixed at the base of the pyramid. A good example was the use of responsive

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regulation by the Australian Tax Office to reduce illegal profit shifting, for example into tax havens, a practice involving pharmaceutical companies. The responsive regulation strategy reduced regulatory costs and litigation costs for business, while raising an extra billion dollars in tax for every million dollars spent by the tax office on the new programme.\footnote{Braithwaite J (2005), \textit{Markets in Vice, Markets in Virtue}, New York and Sydney: Oxford University Press and Federation Press, pp. 89–97.}

There is however a paradox in how this is achieved. If we lop off the top of the pyramid of sanctions, we will be less effective in driving most of the regulatory action down to the base of the pyramid. This is because if all we can do is to escalate deterrence from a slap on the wrist to slaps on both wrists, if there is no serious risk to a firm’s future when it refuses to meet minimum medical standards, it can find a litigious approach to the regulatory game attractive. Regulation will then be contested in adversarial confrontation, at much greater cost, in the middle of a truncated pyramid which has no tough measures at its peak. The paradox is that when honest firms see that dishonest firms are confronted with sharp sanctions at the peak of a pyramid, their voluntary commitment to negotiated problem-solving goes up. They are given incentives to mobilize their managerial creativity by crafting cost-effective solutions at the base of the pyramid. They will be less inclined to play the regulatory game litigiously. The argument is that static cost-benefit methodologies will miss the opportunities for cheaper and better solutions that can come from dynamic regulatory designs. Deterrence is achieved dynamically rather than passively. It is not the passive weight of the expected punishment costs of a static penalty regime that does the work. Deterrence is achieved dynamically through escalation.\footnote{Contemporary criminological theorists of deterrence argue for the virtues of dynamic concentration of deterrence. See Kleiman M (2009), \textit{When Brute Force Fails: How to Have Less Crime and Less Punishment}, Princeton, NJ: Princeton University Press; Kennedy DM (2009), \textit{Deterrence and Crime Prevention: Reconsidering the Prospect of Sanction}, New York: Routledge. A meta-analysis of studies of the effectiveness of dynamic concentration suggests some effectiveness with common crime, see Braga AA and DL Weisburd (2012), ‘The effects of focused deterrence strategies on crime: a systematic review and meta-analysis of the empirical evidence’, \textit{Journal of Research in Crime and Delinquency}, \textit{49}, 323–58.}
8.6 RESTORATIVE JUSTICE AS PART OF A PYRAMID OF STRATEGIES

What do we do when a company offers the ritual sacrifice of an executive for a corporate crime, claiming that this executive is a rogue manager held in contempt by top management? One response is for the regulator to say, "We are relieved to hear that management is as scandalized by this as we are. So we would like to sit down with the entire top management team to discuss it with the 'rogue executive' to see if we can put in place protections against this ever happening again." If the restorative justice conference results in credible reform, the regulator might be persuaded against pursuing criminal charges against the firm and its leadership. If the problem is that the "rogue executive" was in fact a normal executive enacting the normally corrupt culture of the firm, then we can expect this executive (and the supporters whom the executive is encouraged to bring to a restorative justice process) to say that their conduct was normal in the culture of the firm.

Often, in this situation, the fall guy will be able to call upon the support of retired former supervisors or of some angry friends within the firm or among the company's auditors who will speak the truth. This is a possibility because of our finding that at all stages of its history the pharmaceutical industry has possessed some socially responsible executives who have been more committed to the professional values associated with medicine and pharmacy than to the values promoted in marketing spin. Particularly when such individuals retire, we believe that the restorative justice conferences which they are invited to attend in support of their former employees who are being scapegoated will give them an opportunity to expose the corporate culture problems that are the deeper sources of law breaking. This may lead to the discovery of wider patterns of corruption in the company. At this point the regulator might well demand a self-investigation report led by a credible outside

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33 For details on how restorative justice conferences are convened, see Braithwaite J (2002), Restorative Justice and Responsive Regulation, New York: Oxford University Press.

counsel. This might name all the individuals in the firm who have particular levels of responsibility (some criminal, some less than criminal) for the pattern of corruption, followed by evidence of credible internal disciplining of those culpable, even at the highest level, provision of compensation to victims and implementation of reforms to the compliance system to provide a guarantee against recurrence. The report on corruption at Gulf Oil by distinguished outside counsel John J McCloy, commissioned in the shadow of the threat of criminal enforcement for bribery, provided the model in the corporate crime literature of such a report commissioned and funded by the corporation itself. The McCloy report resulted in a deluge of adverse publicity for the company, hastened the resignation of senior executives named in it, and triggered substantial reforms of corporate operating procedures.

Brent Fisse and John Braithwaite have proposed that when the corporate self-investigation report is not developed credibly, or when scant change occurs in response, criminal prosecution of the corporation and of all individual executives believed to have individual criminal responsibility should be undertaken. It is no bad thing that this will prove necessary from time to time. The occasional case, at the peak of the enforcement pyramid, in which a CEO goes to jail, can induce many an individual in the industry at lower levels of the pyramid to behave more responsively. Pharmaceutical regulators may not need to launch major criminal cases every year to accomplish the image of invincibility that they currently lack.

In the very worst cases of corporate crime, one may be obliged to conclude that the industry would be better off were the firm not to exist at all. It would be better for its socially useful products and activities to be taken over by more responsible owners. Especially in developing countries, there are firms that do an amount of damage to human health that outweighs whatever health benefits they confer on society. Corporate capital punishment, by withdrawing the licence of such firms to sell medicines, not only directly improves health, it shows everyone in the industry that a licence to sell medicines is not a right but a privilege that must be earned by diligent stewardship of the public health. It shows that failure to deserve the privilege of a licence is a slippery slope that can

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lead to a sticky end. That sticky end is corporate capital punishment in the form of withdrawal of its licence to sell medicines. Where the firm does house R&D programmes with the promise of future health breakthroughs, it can be reorganized under a completely new management team or be forced to auction its business to a competitor with sound management.

This form of corporate capital punishment has indeed on occasion been used, notably in the regulation of the nursing home industry in Australia, the United States and the United Kingdom. Even with the much less extensive corporate power of the nursing home business as compared with the pharmaceutical industry, the approach has only rarely been adopted in that sector because it is politically so difficult. In the reorganization of a delinquent nursing home, a new provider must be found who is willing to take over the care of affected elderly residents. Failing that, the state must put the home into public receivership and appoint a new management team to organize the care of residents. Even rare use can be sufficient to deliver on the promise of the pyramid. This is the promise that the regulator will do whatever is necessary, right up to corporate capital punishment, to secure the interests of public health.

Where there is no tough enforcement capability at the peak of the pyramid, defiant firms have an incentive to fight regulators in the courts, secure in the knowledge that the worst thing that can happen to them is the imposition of some mild sanction at the mid-level of the pyramid. The irony is therefore that the capacity to escalate to really tough enforcement when necessary enables more of the regulatory game to be played cooperatively, educatively, at the base of the pyramid. Once responsive regulators have reacted to the firm’s unwillingness to reform by escalating their response up the pyramid, a proper response by the firm will cause the responsive regulator to de-escalate its measures towards the base of the pyramid of sanctions. At this point the regulator will look for opportunities to detect such exemplary improvement as can move the firm up the pyramid of supports.

Responsive regulatory theory thus involves a presumption in favour of starting at the base of the regulatory pyramid and then only moving gradually up the pyramid if the firm does not fix the problem, repair the harm and put policies in place to prevent recurrence. This, however, is only a presumption. On occasion it may need to be overridden. If a production line is sending drugs of dubious sterility into the market each day, that production line must be stopped immediately, before anyone is

37 Braithwaite et al., *Regulating Aged Care*, op. cit.
hurt. When scientific fraud is revealed and it is shown that a drug believed to have vast benefits in fact presents risks outweighing any such benefits, an immediate recall of the entire product from the market must be mandated quickly, even if that leads to the bankruptcy of the firm.

It should be clear by now that a pharmaceuticals regulator should not have just one regulatory pyramid. It will have one for fraud in the safety testing of drugs that includes remedies such as recalls, dismissals of chief investigators of studies and replacement by more ethical scientists, revision of study protocols, and the like. It will have quite a different pyramid for GMPs that will include the implementation of new GMP compliance systems, suspension of work on production lines and even closure of entire factories. It will have a sanction pyramid for misleading marketing that similarly includes measures at different levels, such as the ordering of corrective remedial advertisements. Such a suite of regulatory pyramids can best be developed in collaboration with relevant stakeholders from the industry, from the health professions, and from consumer organizations. Ideally, all these stakeholders should participate together in the debate as different options to be inserted at different layers of the pyramid are discussed. None of the illustrative pyramids in this book are pyramids we would want to defend as the right ones. The right ones are likely to come from that kind of dialogue among stakeholders and from responsiveness to evidence that replacing a particular layer of a particular pyramid with something different will improve it.

It can be a good meta-strategy to signal to the industry that the preferred strategy is based on a preference for moving from education and persuasion up a pyramid of supports and then from education and persuasion up a pyramid of sanctions, where the supports are failing to provide improved health outcomes. If that preferred overall strategy does not deliver major improvements in health outcomes, more radical strategies should be held in reserve. By signalling the contemplation of these more radical options, the regulator might motivate greater industry commitment to enabling the essentially cooperative strategy of the pyramids of supports and sanctions.

8.7 WHEN THE DUAL PYRAMIDS STRATEGY FAILS

Let us now assume for a moment that over a decade or more the holistic approach based on Figure 8.1 has failed to bring about continuous and sufficient improvement in the truthfulness and informativeness of pharmaceutical marketing. The evidence-based regulator will then try a
different overall strategy and will signal its intent to do that long in advance of the failure of the initial strategy. One option for marketing regulation would be to use tax policy to drastically reduce the amount of promotional activity to be monitored. Across all areas of productive activity, some economists have made a case for supplementary taxes on advertising. While advertising often does convey valuable information, these economists believe for a variety of reasons that the amount of advertising in contemporary societies is excessive in terms of what is best for economic efficiency. Part of this economic case is that firms increase sales in two principal ways – by bigger, better marketing, or by R&D to discover products with greater appeal to consumers. Punitive taxes on promotional expenditure would shift investment to R&D as a preferred means of increasing sales. This is because a tax on promotion would increase the comparative returns on the other major route to increased sales, i.e. R&D. In general, more social value is created by increasing investment in R&D on the quality of products than in advertising the sale of existing products.

In the pharmaceutical industry, punitive taxes at the rate of – let us say – 200 per cent on all promotional expenditure could save many lives by shifting industry investment to R&D as well as by creating a pool of public funds to support therapeutic R&D in universities and to support publicly funded provision of information on pharmaceuticals. Note that the industry would be beneficiaries of this expanded public R&D as they would continue to be the best-placed organizations to take the new therapeutic breakthroughs to market. Even so, the industry would be inclined to fear that such a radical solution would substantially shift control of R&D and information from the private to the public sector. Because it is hard to build political support for such radical measures, the best way to put them on the agenda is as an option that only swings into effect if the industry fails to rise to the challenge of continuous improvement in the integrity of its promotion. If the industry wishes to stave off punitive taxes on promotion, all it need do is to demonstrate that each year there is a measurable improvement in the integrity of promotion and in the quality of information getting through to health professionals and consumers. This could for example be measured by a well-designed study of the percentage of professionals and consumers who have specific evidence-based knowledge on the effects of specific

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drugs, and the sources of that knowledge. Such research could be conducted by the state regulator or by academics funded at arm's length from the industry. If the industry can demonstrate that it has brought about an improvement in the flow of effective information, the market will be working and there will be no need to use the tax instrument to steer the market in order to enhance economic efficiency and improve health outcomes.

An even more radical escalation of regulation would involve banning all forms of drug promotion, forcing firms to compete only on R&D and price. The government, in collaboration with the health professions, would take over the task of communicating to health professionals and consumers the information they need to make prudent choices on medicines. While it has proven difficult to ban the illicit sale of (untaxed) tobacco and of illicit drugs like heroin, the ban on advertising them has not proven so difficult. Illicit sales can occur below the radar, but illicit promotion is not much use when it is below the radar. This raises the spectre of the meta-regulatory strategy in Figure 8.2 being communicated to the industry.

All the upper reaches of this pyramid might be dismissed by critics as reflecting left-wing thinking and therefore being politically unrealistic. The industry is however sophisticated enough to understand that what is politically unattainable today may not be beyond our reach 20 years from now if society is faced with a series of future pharmaceutical disasters causing many deaths. All developed economies except the United States and New Zealand have, after all, already banned direct advertising of prescription pharmaceuticals to consumers. It must be said, however, that in the era of internet marketing this ban has less power. It therefore makes sense for scholars who believe that they have a better option than a total ban on pharmaceutical promotion to signal in a book like this that if the status quo continues to fail, and if their alternative approach has after 20 years also failed, a total ban is precisely the option to which policy makers will need to turn. We as scholars might be content to try to persuade our friends in such non-governmental organizations as Health Action International, Public Citizen, Oxfam and Healthy Skepticism that Figure 8.2 is a fair set of options to advocate in the event that one after

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40 And the social responsibility of internet marketing direct to the consumer is one reason to consider the option of a tax on all marketing expenditure to dampen internet marketing.
the other of them fails as badly as the status quo documented in Chapter 3. It may not be necessary to persuade any single government to embrace and signal the pyramid in Figure 8.2. To a limited extent, something can be accomplished by powerless academics communicating the fact that radical alternatives do exist. There is a point in making a credible case for adopting them if over a period of decades more modest reforms prove unsuccessful. That advocacy could cause the industry to worry that the radical remedies might come to be appealing to the electorate. One day in the aftermath of a sequence of drug crises that have angered such an electorate, a single country could pick up these radical ideas. What if these academics are then proved correct, and capitalism does not collapse as a result of the curtailment of advertising? What if pharmaceutical R&D improves in that country and its economy becomes more internationally competitive? And what if at the same time research shows that prescribing habits become more evidence-based and more beneficial to public health as a result of the curtailment of advertising?
Our objective in this section is no more than to give some food for thought to thinkers in the pharmaceutical industry who recognize the historical lesson that a crisis can ripen a moment for reform. We would like such industry thinkers to worry about how one day corporate political campaign donations could be effectively banned, and then to worry about the "what ifs" in Figure 8.2.

We have limited our considerations in this section to the issue of promotion, taking this as illustrative of possible policy approaches. However, in the other fields discussed in this book, we similarly suspect that keeping a radical spectre seriously alive in the minds of industry thinkers could motivate them to make capitalism work more ethically. A single example relates to the clinical testing of drugs, where the creation of a public institute to take over clinical testing of drugs from the pharmaceutical industry is a reform option that has already proved worthy of discussion. Testing by a public institute would probably be superior to the stewardship that the industry shows over its contracting of clinical trials.

We should also like to persuade non-governmental organizations concerned with public health, as well as you our reader, to perhaps consider joining us in causing those already worried within the pharmaceutical industry to develop their worries in just these ways. In response, the industry might do something to ensure that more modest reforms work. Our job in universities is not simply to come up with policies that our governments will find palatable today. It is also to be visionary in inspiring responsiveness in civil society with bold evidence-based approaches to reform that might be realized by some future generation that is less timid than our own.

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42 In this section we have really been discussing the idea of a pyramid of regulatory strategies as a complement to pyramids of specific supports and sanctions. See Ayres I and J Braithwaite (1992), *Responsive Regulation: Transcending the Deregulation Debate*, New York: Oxford University Press, pp. 38-40. The evaluation of responsive regulation works by evaluating holistic packages of pyramid strategies in comparison with alternative packages and also by evaluating changes to particular layers of particular pyramids.
9. A responsive criminal law of pharmaceuticals

9.1 CRAFTING JUST VULNERABILITY TO THE CRIMINAL LAW

We have argued that unethical, reckless, fraudulent conduct in the pharmaceutical industry should be made more vulnerable to the criminal law. The pharmaceutical industry should be more accountable to the criminal law because there is a massive corporate crime problem here that causes more harm than all the crime problems currently dealt with by the police. More fundamentally than that, we wish to ensure this vulnerability to the criminal law because we believe (based on the numbers discussed in Chapter 7) that it can work by saving millions of lives worldwide among our generation’s children and grandchildren. The criminal law has profound symbolic power in all societies. John Braithwaite saw this power in action during his decade as a part-time Commissioner with Australia’s national antitrust and consumer protection agency. He would see the shock when during a restorative justice conference he put the question: “Gentlemen, are we taking this seriously enough?” and then added emphatically: “What we are talking about here is a crime.” Having in this way gripped the attention of the participants, he and his colleagues then preferred to deal with the issue at hand as a problem to be solved, with consumers to be compensated and compliance systems calling for improvement, rather than as a matter of devising and implementing appropriate punishment.

The argument underlying the theory of restorative and responsive justice is that the criminal law has greater power when it is experienced as a threatening element in the background rather than as a threat that is made directly to a corporation. It has less power when it is used

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1 In the restorative justice conferences in which he was involved, the alleged offenders always happened to be male.

2 The question of the punishment to be imposed was however always on the table as a justice claim, open to debate among the stakeholders.
frequently with full force. The sword of Damocles is a powerful thing; but if it is actually used to excess it quickly blunts, especially as it smites powerful actors clad in suits of armour. If, on the other hand, it is used only occasionally with swift and awesome symbolism, it can gain the attention of those who normally regard themselves as being elevated above mere threats from the state. The credibility that the criminal law lends to regulators in the course of negotiations can motivate business leaders to engage with a more cooperative, problem-solving and strength-building form of social control.

This is why we opened our analysis in Chapter 8 by considering the paradox of the pyramid of sanctions. When the pyramid on the right side of Figure 8.1 has the potential to escalate to a high peak of punitive enforcement, it can drive most of the action in business regulation down to the cooperative base of the regulatory pyramid. Better than that, it can drive the regulatory action across that base to the pyramid of supports on the left side of Figure 8.1. In the pyramid of supports, we reduce deadly risks by identifying strengths and expanding them until strengthened institutions and strengthened individuals ultimately absorb the risks and solve them. In the long run of history we save more lives in this way – by building on the great scientific strengths and the deep reservoirs of ethical purpose within pharmaceutical companies, in the health professions, in research institutes and in universities, in order to invent new remedies.

The evidence advanced in the present volume makes it abundantly clear that we are confronted with many specific abuses in the pharmaceutical industry that must be dealt with effectively, with victims who need to be compensated and with specific dangers that must be eliminated. Faced with such abuses, we must also, as has been said, "pick important problems and fix them". The theory of the twin pyramids of supports and sanctions is that by having credible vulnerability to criminalization towards the peak of the enforcement pyramid, we can cause both the problem-solving pyramid and the strengths-building pyramid to operate more effectively. Lop the top off the pyramid of sanctions and regulatory history shows that the elite of the business world will choose to game the regulator in litigious cat and mouse encounters at the

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adversarial mid-level of the pyramid of sanctions. The reason is clear: when tough criminal sanctions are lopped off the top of the pyramid, the state will find itself in a deterrence trap. Problem-solvers in matters of health and safety will be pushed aside by legal game players who earn good fees by urging business leaders to push regulators up their truncated pyramid until they buckle. Alternatively, big pharma may decide to pressure regulators until their political masters become nervous. The paradox of the pyramid is that awesome criminal powers that are in their nature threatening but rarely threatened (let alone used) induce a less adversarial regulatory culture.

9.2 PARALLELS WITH THE GLOBAL FINANCIAL CRISIS

This is not to say that criminal enforcement is the most potent sanction at the peak of the pyramid of sanctions. Withdrawal of the licence held by a manufacturer to sell medicines can be more potent. This is effectively corporate capital punishment, which of course constitutes a greater threat than imprisoning selected managers. In a sense, temporary socialism is the ultimate remedy: the state takes over a dangerous company and puts new managers in place to salvage the good things which it contributes in the midst of the wreckage that it also causes. The 2008 global financial crisis should have taught us that no capitalist enterprise should be too big to fail. Iceland perhaps took a sensible approach in allowing its banks to collapse, thereby obliging their shareholders (rather than the country’s taxpayers) to bear the losses. The President of the United States is in a different situation from the Icelandic leadership, but he too must be able to look Wall Street’s masters of the universe in the eye and declare that he is prepared to let some of them go under. He must also be able to say that he is willing to resort to what is in essence temporary socialism (though he is unlikely to use the term) to socialize the losses of a critical capitalist enterprise like General Motors and to dismiss the CEO and install a new one while attaching strings to taxpayer funding, such as an obligation to build greener cars that will secure better long-term sales in a greener economy.

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In the history of pharmaceutical regulation, countless small manufacturers (who have often in effect been “bathtub” manufacturers but who competed with big pharma) have been driven out of business by regulators. Indeed, big pharma frequently created the political demand for such action, particularly when these small manufacturers were found to be counterfeiting their products. Big pharma itself has been immune from corporate capital punishment. Our argument is not that any member of the big pharma club should lose its licence at this point in history. It is that they should not feel themselves immune from corporate capital punishment, for the same reason that the big banks no longer feel immune to it. Banking was only the second most profitable industry sector in late twentieth century America and into the early years of the twenty-first century. The most profitable was the drug sector. The success of both these industries was based on their success at capturing government elites and the policy debate in ways that protected their interests.

9.3 HARNESSING THE SYMBOLIC POWER OF CRIMINAL LAW

The moral issue here is that when our elected representatives vote for a law that defines a form of conduct as a crime, there is profound normative power in that legislative act. It means that this kind of conduct crosses a threshold of immorality beyond which the state can as a consequence of wrongdoing take away from an institution the fundamental freedoms that it ordinarily enjoys. For most citizens, who may be prepared to engage in all manner of lying and cheating in their daily lives, the notion of actually committing a crime and thereby becoming a criminal is most of the time unthinkable. When others do us grave wrongs, we often do wrong back to them. As a rule, however, we do not murder them. That is not because we weigh up the risks of being caught and the likely punishment for the murder. The reason we do not solve the problems posed by our enemies by murdering them is simply that to commit murder is for us unthinkable; it has no place whatsoever on our deliberative agenda. To put it differently: the criminal law has rendered murder unthinkable for us. Such “unthinkability” is attained when the criminal law is in good working order. Sadly, the criminal law is not in such good working order with respect to the pharmaceutical industry. We have shown that the sad litany of wrongdoing documented in this book is indeed thinkable for the elite of the pharmaceutical business.

What is the basis for the criminal law’s ability to render murder unthinkable for us as private individuals? Quite simply, it depends on the
fact that the criminal law of homicide is legitimate and is viewed by citizens as a normative order from which no one is immune. The normative power of the law against homicide does not depend on its consistently incarcerating (or executing) all detected murderers. That is why a country such as Japan could have about the lowest homicide rate in the world for much of the late twentieth century when only 27 per cent of murderers served prison time. When compliance with the law is based on the unthinkability of criminality, as opposed to a calculation of the costs and benefits of compliance, the probability of punishment does not determine compliance.

9.4 THE NORMATIVE THEORY: WHAT CONSTITUTES A CRIME?

Our argument is that the unthinkability of corporate crime in the pharmaceutical industry has up to the present been only weakly attained. Occasional criminal enforcement is needed to correct this shortcoming. A large proportion of the misconduct that we have documented in this book is defined as criminal under the laws existing in some or most of the world’s nations. We find attractive the distinction which US law makes between negligence, which invokes only a civil remedy when injury is caused, and recklessness, which invokes criminality. Most of the unethical conduct of concern in this book is not intentional crime, but it does amount to something worse than mere civil negligence. Black’s Law Dictionary defines mens rea in the US based on recklessness as “Conduct whereby the actor does not desire a harmful consequence but ... foresees the possibility and consciously takes the risk.” We have found empirically that much corporate crime in the pharmaceutical industry involves less than intent but more than negligence in the sense that it involves “willful blindness”.

We saw this particularly clearly with the widespread bribery in which 19 of the 20 largest US pharmaceutical companies were shown to have

8 English law makes a similar distinction between ordinary negligence and “gross negligence”.
indulged in the past.\textsuperscript{11} CEOs were often in effect saying, "Do whatever you have to do to get that contract, but don't tell me how you do it". The combination of this kind of wilfully blind instruction and the creation of off-the-books slush funds that allowed underlings to access cash to stuff in plain envelopes was the making of an industry pattern of wilful blindness. That wilful blindness was criminal in law. Yet no executive of any of these 19 multinationals went to prison in any of the dozens of countries where they paid these bribes. Few crimes could be worse than bribing a health minister to guarantee marketing approval for a drug that had failed to pass muster for marketing approval in other more prudent regulatory systems. Most of the pattern of bribery involved less serious crimes such as paying a hospital administrator to order drugs from one company rather than another. Yet in the discourse of the 1970s all these forms of bribery were referred to as "questionable payments". Society's failure to use terms that clearly pointed to serious criminal bribery devalued the moral authority of the criminal law. Australia has experienced the same problem with corporate tax evasion through transfer pricing that artificially shifts profits into low-tax countries or tax havens. While this is very often a crime as a matter of law, and is sometimes prosecuted criminally in other countries such as the United States, in Australia it is always treated as a "tax dispute". The "tax dispute" is resolved by means of a tax settlement under which the firm in question voluntarily pays an additional sum. No company from any business sector has ever been prosecuted criminally in Australia for tax evasion achieved through transfer pricing. As a consequence, what would happen to an Australian tax official who sat down with pharmaceutical executives in a transfer pricing dispute and said "Gentlemen, are we taking this seriously enough? What we are talking about here is a crime"? They would be laughed at. That laughter would be a symptom of regulation that has failed to harness the normative power of the criminal law.

Fraud in testing the safety or efficacy of a drug is a crime in all countries as is bribery and counterfeiting. Cartels, price-fixing conspiracies, and other forms of monopolistic behaviour are labelled as criminal to different degrees in most countries and not at all in some. Breaches of the standards of Good Manufacturing Practices and Good Laboratory Practices are regarded as criminal in some countries, but as mere breaches of administrative standards in others. Misrepresentation in

pharmaceutical advertising or promotion is conceived as a form of
criminal fraud in most countries, but not in all. Insider trading on the
stock market is a crime in most nations today, but in most of these
countries it was not so viewed in the 1960s. All nations criminalize tax
fraud, but the lines distinguishing criminal evasion from illegal civil
avoidance and legal avoidance are drawn quite differently in different
countries. Most nations criminalize some of the morally least serious
breaches of tax law, such as failing to lodge a required tax return on time,
while treating clever and morally egregious multi-million dollar tax
“avoision” as a matter calling for a civil penalty.

Readers will have noticed that we have rarely paused in the course of
this text to consider the legal status of a particular form of misconduct at
a particular place and time. The reason is that it is not the purpose of this
book to provide a critique of the manner in which different countries
have drawn the dividing line between criminal and civil law. Our view is
that reckless conduct in the testing and the manufacturing of drugs,
misleading marketing of medicines, antitrust offences, securities viola-
tions and tax evasion should all be underwritten by the special moral
authority of the criminal law, in the way that the laws of most nations do
provide, because they are all so important to freedom from domination. It is clear that the scope of the criminal law must not be carried to
unreasonable extremes; an offence such as the late submission of a tax
return, which many countries do criminalize, should be a matter carrying
an administrative penalty (in a category comparable to that of library
fines); there is obviously a moral difference between returning a book
late and burning down the library. Overreach of the criminal law to
embrace acts or omissions that citizens do not see as grossly improper
and antisocial is dangerous for society because it erodes a priceless
normative asset, namely the unthinkable of criminality in the hearts of
citizens.

12 For a discussion of how to decide what to criminalize on the basis of
maximizing freedom as non-domination (republican dominion), see Braithwaite J
and Pettit P (1990), Not Just Deserts: A Republican Theory of Criminal Justice,
9.5 RETHINKING THE DETERRENCE OF CORPORATE CRIME

The economic theory of crime, particularly associated with the Nobel Prize-winning work of Gary Becker,\(^{13}\) views an increase in the severity of punishment as the best way to make it irrational to commit crime. Increasing the certainty of detection is viewed as less cost-effective than imposition of longer sentences since increasing the detection rate is very expensive, requiring large numbers of extra police.

Evidence-based criminology and behavioural economics have reached exactly the opposite conclusion. Perceptual deterrence studies find that people’s expectations regarding the certainty of punishment is a much stronger and more consistent predictor of whether they will engage in crime than their expectations as regards the severity of such punishment.\(^{14}\) Indeed, the perceived severity of likely punishment rarely has any


predictive power. People have a general dread of severe punishment for wrongdoing, but ten years in prison does not seem twice as bad as five; both seem fairly terrible. This is one reason why introducing capital punishment is not the way to reduce homicide - life imprisonment and execution both seem extremely dreadful if one is being rationally calculative about a contemplated murder. Another reason why increasing the severity of punishment does not as a rule work is that people are generally poorly informed as to the average degree of punishment associated with particular crimes. While most individuals have an appropriate fear that if they are convicted of a crime the consequences will be awful, many commit crime because they believe they will not be caught. In a nutshell, this is why many criminologists today conclude that the evidence is for "less prison and more police" (or at least more police who engage in sensible detection and prevention work). 15

Another empirical matter which conventional economic theory in the Becker tradition ignores is that detection without punishment can often be very effective. The literature on regulatory inspection shows that inspection can significantly increase compliance even when the expected penalty approaches zero. 16 The reason is that in our working lives we often know that there are certain things we should not do - such as leaving a filing cabinet wide open since that can constitute a safety risk. When a safety inspector taps us on the shoulder to remind us that we should not do such things, we call ourselves to account; and we say, "That's right - I should not do that. I was being careless and thoughtless". The tap on the shoulder from the inspector reminds us of our

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15 See the 2011 special issue of Criminology and Public Policy on 'More police, less prison, less crime?' (2011), Criminology and Public Policy, 10(1).

obligations; we feel embarrassed that we were not meeting them and our conduct improves in the aftermath of the reminder.

Standard economic theory also ignores the possibilities for extremely low-cost detection work. The Australian Competition and Consumer Commission was at one time responsible for receiving complaints about misrepresentation of interest rates to consumers. The complaints were many. Interest rate misrepresentation was common. At Commission meetings when reports of large numbers of such complaints were received, Commissioners would sometimes declare that these were only minor crimes as compared with some of the major breaches of the relevant Act having large economic consequences; there were insufficient resources to prosecute so many minor breaches, each affecting only small numbers of consumers. An alternative view that sometimes prevailed when certain Commissioners pushed it was that when a few complaints of interest rate misrepresentation were received against one company, a member of the Commission staff would call the company, posing as a consumer, asking to be advised of the offending interest rate. After the misrepresentation had occurred, another Commission officer would call both the person who made the misrepresentation and senior management of the company to advise them that on a certain day at a certain time a particular misrepresentation was made to a named consumer. Further it would be pointed out that this was not the only such complaint the Commission had received. The company would be asked what it would do to ensure that such non-compliance ceased. There would be no punishment, merely a warning. This shot across the bows was based on a cheap form of detection – two phone calls – and was probably a cost-effective form of enforcement. It would normally lead to a decline in this kind of complaint about the company. If it did not, responsive regulation would of course call for a more expensive face-to-face follow-up.

Rather than punishment, detection followed by a serious conversation as to why the wrongdoing must stop is the most effective technique for improving compliance with the law. The power of detection can be further increased by bringing some ritual seriousness to the conversation. A restorative justice conference at which the CEO is asked to make solemn commitments in the presence of a large group is one way of doing that. Conversational regulation with companies works in many instances because business actors have multiple selves. They certainly

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have profit-maximizing selves that will tend to be their dominant selves when they are in their business role. However, they also have incompetent, irrational or disengaged selves that are responsible for much of their reckless conduct as pharmaceutical executives. On the positive side, they generally have socially responsible selves that help them to get out of bed and go to work each morning in the belief that they are making a contribution to the public health. Sometimes they have professional selves as doctors, pharmacists or environmental engineers that bring with them a certain pride in bringing to bear professionalism in order to advance the public health. Some have in addition religious beliefs that constitute radical alternatives to their profit-maximizing selves.

Responsive regulation is a strategy for enticing executives to put their best self – or one of their various socially responsible selves – forward. At its best, responsive regulation generates enough detection to induce ethical habits of compliance that render corporate crime as unthinkable to executives as murder is for most citizens. The major challenge, as we concluded in Chapter 7, is the complexity of the science, the organizational complexity and opacity, the inter-jurisdictional complexity of transnational operations and the complexity of the accounts, all of which render it difficult for outsiders to detect crime and prove it beyond reasonable doubt. We turn to this challenge in Chapter 10.

When we were writing in the 1980s we believed that an activist tort bar and whistleblower protection laws might do a lot of the work of supplying the needed step up in detection. We conclude now that these hopes were misplaced. Whistleblower protection laws have as a rule failed to persuade whistleblowers that their careers and possibly their lives will not be ruined by telling victims the truth as regards the wrongdoing that has victimized them. They contemplate the suicide in the family of Stanley Adams (*Roche v. Adams*) and ponder whether a similar fate might not befall themselves. There are however signs of hope in this regard. In Chapter 10, we encounter that hope in the successful cases brought against big pharma in the United States under the False Claims Act. Enforcement under this law has dramatically increased detection rates for particular kinds of crime.

Viewing the issues more broadly, we can take a different approach to the criminal law paradigm of how compliance with law is achieved. Consider the regulatory challenge of persuading drivers to proceed safely on highways. Most drivers comply with the highway laws most of the time because of their good compliance habits. Some of those habits, such as driving on the correct side of the road, are more solidly based than others because the tightly regulated architecture of road building inculcates it and because detection is swift at the hands of drivers approaching
from the opposite direction who blow their horns at us if we fail to obey the rule. Sometimes, perhaps quite often, we may cheat by breaking a speed limit as a rational calculation to achieve the objective of reaching a destination more quickly. Quite often we also break the law because we are careless, tired, and thinking of other things. Traffic regulation has been relatively successful in improving the architecture of roads and the design of cars to make compliance more habitual, as in the habit of clicking on the right indicator as we turn the wheel to the right. Educational campaigns have had some success in persuading us to take rest breaks on long trips, to self-regulate distractions from phone calls while driving, and the like. In Australia, speed cameras and random roadside alcohol breath testing have significantly increased the detection of certain kinds of calculative cheating on the rules. Together, all of these things have greatly reduced road fatalities even as road users and usage have increased.

Ross Homel has undertaken important research as to why random roadside breath testing in Australia has saved so many thousands of lives.\(^{18}\) His empirical research concludes that it was not primarily an effect of punitive measures, but an effect of a cultural change in Australian drinking norms, driven by increased detection. When the change was introduced, it was accompanied by a television advertising campaign portraying scenes from a public house in which television personalities intervened to insist on giving a ride home to a friend who had consumed too much alcohol. The campaign urged responsible drinkers to "be a mate" by keeping their friends out of trouble with the new law. According to Homel's evaluation, this and other educational measures in schools, workplaces and the media worked in changing Australian drinking norms, promoting reliance on designated drivers in groups of drinkers, use of shared taxis, and other novel preventive habits. These new habits also brought with them a view of heavy drinking and driving as shameful in the eyes of most Australians in a way that it had not been in advance of a controversial law reform. That reform was not primarily punitive; instead it linked increased detection to informal reminders about new drinking norms. Defiance became shameful for most of the population because the educational campaign was successful in persuading participants in Australia's heavy drinking culture that the new habits were so easy to apply that they could and would be enforced by good mates and caring partners. While in our field we do not have the

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quality of evidence that Homel has provided on drinking and driving, our experience suggests that the introduction of Good Manufacturing Practices (Chapter 2) from the 1970s onwards created many good new habits, and redefined conduct that previously would have been viewed as "sloppy" into shameful breaches of the law.

There are so many examples in crime control of preventive programmes like these that have worked in reducing crime. In contrast, few of the policies based on an increase in the use of imprisonment as a way of reducing the crime rate have proved successful; there is little evidence that societies with exceptionally high imprisonment rates (like the United States, Russia and South Africa) have experienced a reduction in crime rates as a result. In the face of this, one can only disagree with those reformers who regard the imprisonment of pharmaceutical executives as the front-line approach to reducing corporate crime in the pharmaceutical industry, especially since, as we have seen, scapegoating has proved to be a widespread phenomenon in this industry.

An alternative path is suggested by the accomplishments of another technologically complex transnational industry – air transport. During the first half of the twentieth century, flying was an extraordinarily dangerous form of travel. Today, even in the least technologically sophisticated societies in the world, local airlines can move passengers around a country more safely than can road transport. Contrary to what one might have anticipated, it has within only a few decades of experience become safer to fly through the air than to travel across the earth or the sea. That has been achieved even though flying is more intrinsically risky and more technologically difficult than either driving or sailing. Has this been accomplished by imprisoning pilots when they breach safety rules? Quite the opposite. Air safety is distinguished from other domains of business regulation by its almost total absence of punishment. In most countries, pilots and other airline employees are never fined, imprisoned or executed for safety breaches that might have cost hundreds of lives. Rather the philosophy has been that a punitive approach to near misses will lead employees to conceal them. Any attempt to cover up evidence of potentially dangerous episodes has been regarded as constituting a danger to air travellers because it will prevent organizational learning (and transnational learning) about things that can go wrong in a technologically complex undertaking. Pilots are rewarded with expressions of professional esteem instead of being punished by the law when they report near misses that their colleagues can analyse and from which they can learn. Conversely, any attempt to cover up such events is likely to result in punishment and professional shaming. With such a regulatory approach, a cover-up will be regarded as being both professionally stupid
and irresponsible. Pilots, therefore (in contrast to pharmaceutical executives), are less inclined to cover up. In short, the vital need to recognize and learn from latent and emergent hazards in a technologically fast-moving environment needs to be as well recognized in the pharmaceutical business as it has become in the airline industry.

A policy implication is that one must seek to attain early intervention against all kinds of crime, particularly corporate crime, through preventive, participatory conversations. When, therefore, a pharmaceutical regulator or an internal compliance unit becomes aware of any kind of near miss – for example, suppression or fabrication of safety data before a drug has been approved as safe, detection of a contaminated batch of medicines before they reach patients, advocacy of price fixing or bribery within the firm in advance of such a crime being committed – good practice will be to convene a meeting of all stakeholders in the near miss at issue to determine whether this incident reflects a widespread pattern of misconduct, and to consider what might be done to prevent such a near miss from becoming the prelude to a future disaster for patients and/or the company. Within that learning circle, good practice will be to praise those who help the learning process by bringing forward evidence of a wider pattern of wrongdoing and to ignore those who seek to scapegoat those confessing to wrongdoing. The ethos is to learn what the systemic problems and the cultural problems are within the organization, and indeed within the regulatory system, that have led one individual, or many, within the organization to flout their legal obligations. On the back of that learning, the objective must be to build organizational commitment to preventive plans that can protect the public health (and also support the victims of any past wrongdoing). Beyond this, a commitment must be accepted to evaluate whether those plans work and to report publicly on the lessons learnt. In sum, the objective is not to move to punishment from a culture of impunity and denial, but to move instead to a culture of learning (as a first preference). Only if criminality and cover-up persist will escalation up the enforcement pyramid to severe punishment become important. This may ensue sufficiently often to underline the message that criminals will be held responsible for their crimes if they refuse to accept voluntarily responsibility for repairing past harm and preventing future harm. Such instances will suffice to catalyse

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cooperation at the base of the pyramid, fuelled by the fear of criminal enforcement at its peak.

Where the regulatory settings fail to elicit a culture of learning and prevention, *qui tam* is likely to provide the best instrument so far identified to promote detection. That approach will be considered in the following chapter. Reliance on *qui tam* does not mean giving up on restorative justice at the base of the regulatory pyramid. Rather we see *qui tam* as a strategy for forcing detection in order to draw corporations into a restorative justice circle when they seek to pre-empt a *qui tam* suit. Even in a restorative justice process entered to prevent punishment, denial has a chance to give way to apology, recompense and learning.

9.6 VIRTUES OF DUAL-TRACK US REGULATORY STATUTES

While it is hard to find certain aspects of US regulatory culture attractive, we believe that it has done a better job than other systems with which we are familiar in getting right some fundamental principles regarding the relationship between criminal law and regulatory law. The first principle is that where improper conduct is not morally egregious it should not be criminalized, but should be subject only to civil penalties. Second, forms of conduct that at their worst are morally egregious, but that are often wrong without being egregiously wrong, should be subject to a dual civil-criminal statutory framework. Whether a given breach of regulatory laws concerns safety, antitrust or the environment, the US statutory framework generally provides that the regulator can opt to prosecute that breach criminally or civilly. If regulators overreach themselves by filing criminal allegations for breaches that are not egregious, prosecutors are likely to warn them off, and if prosecutors fail to do so, judges and juries are likely to throw out cases that might well have led to sanctions had the civil route been taken. American regulators therefore learn to take the civil route most of the time, saving criminal enforcement for those egregious cases most likely to underwrite the authority of the criminal law. This is as it should be according to our argument. As we have noted

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20 We interpret moral egregiousness within the frame of civic republic political theory as behaviour that crushes the dominion (freedom as non-domination) of others. Yet this of course is just one of many possible normative theories of the highly contested domain of culpability for crime.
earlier, a sword of Damocles that is overused loses its awe as a sword of Damocles.\textsuperscript{21}

The statutory framework of regulatory law in most other countries has not learnt from the virtues of US two-track design. Most regulators from other nations triage the forms of wrongdoing which they regulate into criminal matters, matters that may involve administrative penalties, and undesirable forms of conduct that are not illegal and hence are trusted to self-regulation, education, negotiation and persuasion. Legitimacy crises abound across these boundaries. Breaches of Good Manufacturing Practices in some countries are relegated wholesale to the category of transgressions carrying only administrative penalties, since most such breaches are indeed minor. From time to time, however, more serious issues will arise, for example, a case of recklessly contaminated manufacturing that costs a dozen lives. If in such an instance a mere wrist-slapping administrative penalty is imposed, the law may be viewed by citizens as failing them. Conversely, when a form of regulatory offence that has been put in the criminal category is serious, but not greatly so, prosecutors may relegate it to the bottom of their pile of cases, arguing that they have an overload of more serious matters regarding assaults and burglaries. Such a pharmaceutical case may never reach the top of the pile, and the regulator may be persuaded not to send it to the prosecutor at all. If this happens more than incidentally, regulatory law will soon lose its legitimacy since serious offences will have occurred and the regulator will have done nothing. Under the American dispensation, the regulator can in this kind of case stay out of the prosecutor’s hair by going down the civil penalty track. The civil-criminal two-track design permits regulatory enforcement of both greater integrity in terms of justice and greater effectiveness in saving lives.

\textbf{9.7 OPTIMIZING JUSTICE WHILE EMBRACING COMPLEXITY}

When a civil or a criminal case is launched against a pharmaceutical company that is engaging in behaviour causing substantial harm, various dimensions of justice will be at issue. First, there is the matter of justice

\textsuperscript{21} This is argued in Braithwaite, \textit{Restorative Justice and Responsive Regulation}, op. cit., pp. 119–22, on the basis of Lawrence Sherman and Heather Strang’s RISE data that shows criminal offenders randomly assigned to a restorative justice conference have greater fear of future criminal enforcement than offenders randomly assigned to criminal prosecution.
for the victims. These may be many and their suffering severe and persistent. They may be limbless children as in the thalidomide case with which we opened this book; they may be confined to a wheelchair or suffer chronic pain that makes it impossible for them to earn a living. Their priority where justice is concerned may well be to push for a deal with the company that will deliver cash to them and thus render their lives more comfortable. There can be many reasons associated with justice for victims to opt for a speedy negotiated settlement that will get the drug off the market as quickly and completely as possible, rather than launch a protracted criminal prosecution.

It is not unknown for companies that have been cornered by evidence advanced by the prosecution to start believing the propaganda of their own defence, as mouthed back to them by their lawyers. Justice for victims whose claims for compensation are brought only later will be badly served if companies intoxicated by the arrogance of their own defence close their minds to the claims of the victims. A company that has lost its marketing licence in one country may be sufficiently persuaded of its innocence to continue to sell it in other markets where no such legal action has been taken. That is not mere theory; such things have actually happened and are documented in this book.

The justice claims of defendants must of course also be taken seriously. We have seen that these can be acute in a world of “vice-presidents responsible for going to jail”. One must also consider the justice claims of an Australian Aboriginal burglar who says: “You are putting me in jail for stealing a few thousand dollars from this house, while you do nothing to the drug company executives who injured my daughter and cost the community millions of dollars”. At one level, this is justice as proportionality in sentencing. But it has a deeper level that is about distributive justice. For the Aboriginal burglar, it connects to multiple layers of injustice. It connects to the fact that the house from which he burgled was built on land stolen from Aboriginal people. For him, the leniency towards pharmaceutical executives is about the power of white elites to engage with impunity in one form of pillage after another. Our Aboriginal burglar might say to us that Pillage and Impunity would be a nicely ambiguous title for this book.

Finally, a form of justice at issue is restorative justice, the idea that because crime hurts, justice should heal. Many lives are damaged when an organizational crime is prosecuted – victims, defendants, scapegoats, or workers who worry that their place of employment may be shut down because of the crime that occurred within it (even though they themselves had nothing to do with the malpractice in question). One must also consider employees who may be bullied into covering up the crimes of
their bosses, regulators who are threatened politically for pushing ahead with a case against a major firm, other regulators who are vilified for not picking it up earlier, witnesses bullied by investigators and lawyers from both sides, and the families of all of these stakeholders. With a complex organizational crime, the ripples of emotional damage are likely to spread widely. In some cases where the stakes are high, the ripples are so large that the community as a whole becomes a victim as the work of talented research scientists engaged in studies that could lead to the emergence of life-saving drugs is abandoned as a direct result of the criminal process.

In the face of so many serious claims for justice, the jurisprudence emerging from myopic mainstream criminal law seems morally flawed. Extremists may argue that "equal punishment for equal wrongs" trumps other justice claims. In this view, the fact that a serious crime has occurred calls for criminal proceedings that will mandate punishment proportionate to the culpability of the criminal. We would advance an alternative normative stance reflecting equal concern for the claims to justice of all the various stakeholders considered above. Our presumptive preference would be to attempt restorative justice in the shadow of the criminal law, a form of restorative justice drawing on the moral authority of the criminal law. One reason for this is that restorative justice circles are designed to give voice to the claims of all who have a case to advance. Restorative justice circles do not narrow the justice issues towards punitive culpability in the way that criminal trials do, nor do they narrow them to issues of compensation for victims in the way that tort does. They do not funnel and filter justice claims through a legal mouthpiece; all stakeholders are empowered to present their own narratives and evidence of injustice in their own voice. A reason for this is the evidence that this will help their healing; one must never forget that restorative justice can help to heal the hurts associated with the crime.

More important in the context of corporate crime in the pharmaceutical industry is the evidence that in common criminal cases randomly assigned to restorative justice (or compared with a credible control group), the voluntary commitment to repair the harm and to implement

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22 Braithwaite and Pettit, Not Just Deserts: A Republican Theory of Criminal Justice, op. cit., advance an argument for this stance in terms of republican normative theory. Braithwaite, Restorative Justice and Responsive Regulation, op. cit., provides an analysis of why and how restorative justice supplies the procedures with the best prospects of optimizing the joint pursuit of the justice claims of all affected stakeholders in a crime.

an agreed programme of rehabilitation or reform is much greater in the cases that go to restorative justice. Most importantly of all, where multinational pharmaceutical companies are concerned, the superior voluntary commitment that a process of restorative justice delivers to put things right can mean that the conference signs a commitment to remove a dangerous product or batch not only from the jurisdiction over which the regulator has legal authority, but from every jurisdiction. This includes poor countries which have no capacity to determine whether discredited drugs are being dumped on their citizens.

It is complex and difficult to optimize prevention of future victimization, to support existing victims, to help a company get back to the business of inventing better medicines and meeting the justice promises of the criminal law as an institution. We will only do better in terms of justice when we acknowledge that complexity, when we eschew the simpler, offender-centred justice rubrics of conventional criminal law jurisprudence.

Finally, what are we to say to our Aboriginal burglar who is so resentful of the (mostly) soft justice meted out for this white, white-collar pillage? We look forward to the day when we can say to him that the presumptive preference of the justice system in their case as well as in that of the white-collar criminal is to try to make restorative justice work, and only to move up the enforcement pyramid when after many attempts it still fails to make a problem-solving circle succeed. When analysis of the dilemmas of corporate crime in the pharmaceutical industry causes us to extend restorative justice not only to Aboriginal Australians, but to the almost equally disadvantaged minorities that disproportionately fill the prison cells of Europe, North America and beyond, it may cause us to

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tear down some prisons built to house them. If that happens, then it will have done a double service to social justice.

9.8 ETHICAL LEADERSHIP FROM THE INSIDE

This chapter opened by noting that one strength of the pharmaceutical industry lies in the fact that so many ethical people work within its walls. Most of the voices which advocate reform do so from outside – as regulators, or as citizens putting pressure on regulators or directly on specific companies. That activism is something we can all be part of by supporting advocacy groups such as Oxfam, Health Action International, Public Citizen, Healthy Skepticism, Consumers International and Médecins sans Frontières. We will be well advised to understand, however, that such outside pressure is most likely to have an influence when it strengthens the hand of ethical professionals who within the pharmaceutical industry struggle for continuous improvement and dedicated service to public health.

One way to grasp why better laws and better enforcement are only a part of the solution is through the thought experiment of imagining a world where regulation was so total and perfect that it was impossible for a pharmaceutical executive to behave unethically. The problem in such a world would be that it would also be impossible to behave ethically. Ethics would never be tested. Ethical judgement is something that withers when it is not matured through use. That is part of the case for responsive pyramids that *enculturate* trust, while they *institutionalize* distrust. At the bottom of regulatory pyramids, the norm is one of trusting managers to hone their ethics through use, and through ethical deliberation with their peers. Criminal exploitation of trust will however trigger an inexorable escalation up a pyramid of checks and balances. One hopes that if conduct becomes so exploitative inside a company, enforcement will expel the criminals. Yet we may also hope that ethical advocacy will in the meantime have nurtured and inspired a pool of ethical and innovative professionals ready to step into their shoes.

There are many practical guides as to the steps that need to be taken to build up that pool, such as the “10 Steps to Ethical Decision-making in Biobusiness” identified by David Finegold and his co-authors.25 Our mission in this book is not to present management with a “how to” guide

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for the cultivation of corporate ethics. It is about how to create a regulatory responsiveness that nurtures that journey of learning. The paradox of our analysis is the argument resumed in Chapter 10 that ethical responsiveness can be nurtured by regulators having access to tougher criminal enforcement tools, particularly *qui tam*, which gives whistleblowers a share of penalties, equity fines, and restorative justice conferences designed to transform Corporate Integrity Agreements into ethically serious documents.
10. Privatizing enforcement

10.1 LAW REFORM FAILURES

In their writings of recent decades, Graham Dukes and John Braithwaite have both argued that tort law has proved to be more effective in controlling corporate crime in the pharmaceutical industry than has criminal law.¹ They are now more doubtful about the accomplishments of purely privatized enforcement by victims based on tort. When Braithwaite was writing Corporate Crime in the Pharmaceutical Industry in the early 1980s, there had still been very little criminal enforcement directed against pharmaceutical companies, even for the most egregious of criminal conduct he documented. Yet there had been some tort cases in which discovery of documents by lawyers working for patients who sued for drug-induced injuries revealed recklessness and major fraud by multinational corporations. In some of these cases the punitive damages imposed by the courts were much higher than could ever be attained in the criminal cases of that era. In the three decades since then, pharmaceutical industry profits have increased much more steeply than worldwide tort settlements, to the point where the occasional need for a secretive tort settlement with an injured patient has become an acceptable cost of doing business. In the classic case of Grundberg v. Upjohn,² for example, heard in the United States and relating to injury induced by the sleeping remedy triazolam, in which one of the present authors served as an expert witness for the plaintiff, the company settled in 1991 for a sum amounting to many millions of dollars; a condition imposed by the firm was that the actual sum should remain confidential; many similar settlements relating to the drug followed.

Particularly in the aftermath of “tort reform”, which made mass tort litigation more difficult, tort was left with little capacity to change industry behaviour. The industry also became much more adept at using legal professional privilege and at avoiding the creation of the sort of incriminating documents that a previous generation of tort lawyers had been able to extract from companies.

Pamela Bucy has been the scholar who has shown across a range of areas that US legal reforms to allow for private citizen suits have achieved very low success rates. As a result, citizens have become utterly discouraged about resorting to them. These reforms include provisions for private enforcement under the Consumer Product Safety Act, the Americans with Disabilities Act, the Civil Rights Act 1964, the Electronic Communications Privacy Act and a variety of other consumer protection and environmental protection statutes. The corporate crime enforcement community once had high hopes for the kind of private enforcement of the Racketeer Influenced and Corrupt Organizations Statute (RICO); Bucy was however able to show that by 2002 there had been only three victories in 145 civil RICO cases.

Assisting large numbers of citizens who had been injured in the same way by the same company to organize collectively to sue through class actions was a reform that was worth a struggle in the latter decades of the twentieth century. However, even when citizens did win in these cases, the greater part of the damages secured did not always benefit the victims; more dollars frequently went into the pockets of lawyers and the administration of the tort system. The idea was right, that there was more entrepreneurial legal talent capable of taking on big business in the private bar than among the ranks of public prosecutors. The problem was that these tort lawyers achieved a very low success rate in getting the inside information that was necessary to prove that patient injury resulted directly from the company’s failing to comply with some provision of

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4 Peter Cane, for example, cautions with data from the Pearson enquiry in the UK: “according to the Pearson figures [£377 million in 1977 currency values], the administrative expense of the system as a whole amount to about 85% of the value of the sums paid out, or about 45% of the total costs of the system. So (if we ignore insurers’ investment income) we can say that about 55 pence of the insurance premium pound is paid out to injured victims, and 45 pence is swallowed up in administration”. See Cane P (2006), *Atiyah’s Accidents, Compensation and the Law*, 7th edition, Cambridge: Cambridge University Press.
regulatory law. Whistleblower protection laws of different kinds proliferated throughout the western world to assist with this challenge. These laws however also failed to be game changers because the protection that they afforded was never sufficient to change the reality that being a whistleblower against a major organization was a career-ending move.\(^5\) Worse, whistleblowers suffered such vituperation from former workmates that they became depressed and even suicidal.

The law reform that has made a difference in the United States since the late 1990s, but nowhere else to date, has been the 1986 series of amendments to the False Claims Act. This chapter argues that these reforms should be generalized and possibly linked to other radical reforms like equity fines that would put more teeth into Corporate Integrity Orders (or corporate probation as one used to say in the corporate crime literature).\(^6\) The lesson of the last four decades of enforcement against corporate crime in the pharmaceutical industry has been that society was right to seek reforms that would harness the entrepreneurial talent of private law enforcers, but that these reforms failed to provide complementary reforms to the provisions on whistleblowing that would succeed in extracting incriminating inside knowledge. What was needed was not exactly a privatization of enforcement against the pharmaceutical industry, but an effective form of hybridity between private and public enforcement. The False Claims Act is on a trajectory to becoming a game-changing private-public enforcement hybrid. If other legal systems are to follow the American example, they will have to undergo as radical a reform as the False Claims Act. It is however possible to follow the precedent: even within the United States, elements of the reform have been picked up with tax fraud by large corporations.

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and with Securities and Exchange Commission enforcement (including extension to Foreign Corrupt Practices Act cases under the Dodd-Frank securities law reforms).\(^7\) In tax and securities enforcement, however, while the Internal Revenue Service and the Securities and Exchange Commission are required to share a percentage of penalties with whistleblowers, whistleblowers are not given the right to initiate their own *qui tam* suits.

We will suggest that *qui tam* reform might be even more useful to developing economies than to wealthy ones like the United States. We will argue that analogous reforms might be introduced in many countries to cover a wider array of corporate crimes involving the pharmaceutical industry than are currently covered by this pioneering American legal innovation.

### 10.2 QUI TAM

*Qui tam* is an abbreviation of a Latin phrase meaning, "He who sues as much for the King as for himself".\(^8\) *Qui tam* first entered the law in thirteenth century England. It rewarded private prosecutors by awarding them half the amount of the fines imposed by the courts. During the fourteenth and fifteenth centuries *qui tam* was widely used and abused. Bounty hunters and informers often fabricated evidence and framed suspects to get their payout. English law therefore restricted its use until it became a dead letter, though it was only formally abolished in the twentieth century. President Lincoln revived *qui tam* in the United States with the False Claims Act of 1863, using it to prevent defence contractors from defrauding the Union Army. The Act rewarded private suits for false claims against the government with a bounty. Abuse of this renewed *qui tam* also became rife; again it fell into disuse.

In 1986 *qui tam* was revived in an effective manner for the first time when Republican Senator Charles Grassley of Iowa introduced amendments to the False Claims Act. His amendments controlled abuse in effect by making private prosecutors more accountable to public prosecutors. As a result, after some years during which lawyers learned how to use the new tool and expanded the scope of cases to which it was applied

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\(^8\) *Qui tam pro domino rege, quam pro se ipso in hoc parte sequitur.*
with increasing creativity, the False Claims Act eventually became the state’s primary weapon to fight white-collar crime.\(^9\) \textit{Qui tam} cases filed under the False Claims Act numbered only 33 in 1987, passed 100 for the first time in 1992, passed 200 in 1994, 300 in 1996 and have never fallen below that number since. In the aftermath of the Obama administration’s reforms to the Act in 2009, we are likely to see a surge to higher levels of enforcement again, with wins against pharmaceutical giants under the False Claims Act being many times higher than tort victories. \textit{Qui tam} civil settlements and judgments (not including criminal penalties) passed a million dollars for the first time in 1989, passed a billion dollars in 2000 and remained above that in every year since, apart from 2004, passing three billion dollars for the first time in 2006.\(^{10}\) In recent years recoveries have multiplied largely because of big pharma cases. Fraud against the government’s healthcare system has been the fastest growing arena of \textit{qui tam} suits, accounting now for half the cases and for the lion’s share of recoveries. Jack Meyer has concluded that for every federal dollar spent on investigating and litigating civil False Claims Act healthcare cases, the federal government receives 15 dollars in return, up from eight dollars in the early years of the False Claims Act.\(^{11}\) Recent major cases against big pharma have included: 12

- GlaxoSmithKline: $3 billion in 2012 for illegal promotion of nine different drugs, paying kickbacks, doctoring and fabricating scientific research and articles;
- Amgen: $762 million, including $150 million in criminal penalties, in 2012 for off-label claims and kickbacks in relation to AranespR, which had been used by Olympic athletes; Amgen is the world’s largest biotechnology firm and was the first inventor of EPOs used


by Lance Armstrong (also the defendant in a *qui tam* suit) and other elite cyclists;  

- Pfizer: $2.3 billion penalty in 2009 triggered by lawsuit of six whistleblowers ($1.3 billion criminal fine for bribes to healthcare providers and off-label marketing of various drugs beyond their approved uses and a $1 billion False Claims Act civil penalty);
- Abbott Laboratories: $1.5 billion in 2012, including a $700 million criminal fine for off-label marketing and misleading claims about the safety of epilepsy drug DepakoteR;
- Lilly: $1.4 billion in 2009 ($515 million criminal fine, the rest various False Claims Act penalties) for off-label marketing of ZyprexaR (olanzapine) for the treatment of dementia, mostly in nursing homes, whereas it had been approved only for schizophrenia and bipolar conditions;
- Merck: $650 million civil settlement in 2008 for pricing fraud and kickbacks relating to its products ZocorR, VioxxR and PepcidR;
- Serono: $704 million ($567 million under the False Claims Act; $137 million criminal penalty) for fraud relating to off-label marketing of a drug for the treatment of AIDS;
- Takeda-Abbott (TAP): $875 million ($559 million under the False Claims Act, a $290 million criminal fine) and a "sweeping" Corporate Integrity Agreement for fraudulent drug pricing and kickbacks;
- Bristol-Myers Squibb: $515 million ($328 million under the federal False Claims Act, the rest in six state False Claims suits for illegal remuneration to health care providers, off-label promotion, fraudulent and inflated pricing);
- SmithKline Beecham: $325 million in one of the early major cases in 1997 filed by two employees of SKB and two employees of a competing company;
- AstraZeneca: $355 million in 2003 ($266 million under False Claims Act plus criminal liabilities) in a case launched by the vice-president of sales for TAP Pharmaceutical Products; then $520 million in another False Claims Act case in 2010;
- Bayer: $257 million (civil and criminal) for "lip and stick" relabelling and disposal at concealed discount prices, exposed by a former executive.

This new enforcement clout has been assisted by provisions for heavier criminal penalties than those available in previous decades. As can be seen from the list above, large criminal penalties in big pharma cases have frequently piggybacked on private False Claims Act suits. The more important change has been in the seniority of some of the whistleblowers in the above list of companies who went public to point prosecutors to the places where the bodies were buried inside the formerly secret fortress of the corporation. The large Takeda-Abbott criminal fine arose because a former vice-president of sales, Douglas Durand, filed a False Claims Act complaint against the company. More than that, his status as a senior industry insider also allowed him to win a second False Claims Act suit against AstraZeneca.\(^\text{14}\) Again a successful criminal conviction of AstraZeneca followed in the wake of Durand’s civil suit for its marketing and pricing practices for Zoladex\(^\text{R}\), a drug for the treatment of prostate cancer. In the $3 billion GlaxoSmithKline case of 2012, the crucial insider information was provided by Thomas Gerahty, a former senior marketing development manager for Glaxo, and Matthew Burke, a former regional vice-president.

### 10.3 TOO BIG TO FAIL; TOO BIG TO JAIL; TOO BIG TO NAIL

The most famous whistleblower to launch a False Claims Act suit against his company was Peter Rost, a vice-president for marketing in the largest pharmaceutical corporation in the world, Pfizer.\(^\text{15}\) The 2009 $2.3 billion civil and criminal penalty is the most recent in a sequence of False Claims Act suits against Pfizer involving at least six other whistleblowers. In 2004 Pfizer pleaded guilty to resolve criminal and False Claims Act charges for paying doctors to prescribe its epilepsy drug Neurontin\(^\text{R}\) for conditions for which the drug was not approved as effective, such as bipolar disorder, attention deficit disorder and drug and alcohol withdrawal seizures.\(^\text{16}\) Pfizer has been fined four times for illegal marketing since 2002. The biggest concern in the 2009 case was over the painkiller Bextra\(^\text{R}\), which was promoted by the Pfizer division Pharmacia


\(^{15}\) Ibid.

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and Upjohn\textsuperscript{17} for conditions not approved by the Food and Drug Administration because of safety concerns. The company also promoted usage in amounts beyond those approved by the government. Pfizer withdrew Bextra\textsuperscript{R} from the market in 2005 after it was found to be associated with heart attacks and other problems. In June 2010, Dr Scott S Reuben, whose research helped to establish Bextra\textsuperscript{R} and other Pfizer products (Celebrex\textsuperscript{R} and Lyrica\textsuperscript{R}) as effective, as well as Merck’s now withdrawn Vioxx\textsuperscript{R} (which the FDA associated with 25,000 deaths), went to prison for research fraud.\textsuperscript{18} Reuben mostly fabricated data from non-existent patients for at least 21 journal publications, primarily on acute pain research. These papers have been withdrawn by the anaesthesiology journals concerned. He was paid by Pfizer as a member of its speakers’ bureau on behalf of its medicines as well as receiving Pfizer research grants. He had written to the FDA to lobby them on behalf of the products he had researched. Pfizer was also found in its 2009 False Claims case to have ghostwritten journal articles touting Bextra\textsuperscript{R} that did not disclose the company’s role.\textsuperscript{19}

While this case was pathbreaking, it still reveals a large corporation’s power to manipulate government and the law as considered in Chapter 4. Any company convicted of major health fraud is excluded by law from the Medicare and Medicaid programmes. Prosecutors came to the view that excluding Pfizer from these programmes would lead to the collapse of the company and thereby potentially deprive Americans of many of the valuable drugs that the company produced. The US government therefore essentially conspired in allowing Pfizer to pin the worst allegations against it onto a shell company (devoid of products that could

\textsuperscript{17} Pharmacia incorporated the former GD Searle Corporation of which Donald Rumsfeld served as CEO in the 1970s and which was the subject of Braithwaite’s “reincarnated rats” safety testing fraud case study (in Braithwaite, Corporate Crime, op. cit.). Rats died at one point in the research, but later “reappeared” as live rats.


be affected by a Medicare/Medicaid ban).\textsuperscript{20} Just as certain Wall Street financial houses were too big to fail during the global financial crisis, Pfizer was “too big to nail” during the pharmaceutical fraud crisis that the False Claims Act produced.

As we saw in Chapter 3, the large settlements in these cases mean that the government can generally ask for a Corporate Integrity Agreement and get far-reaching accommodation of this request in the hope this might reduce monetary penalties. These agreements can cut deep or they may be purely ritualistic: Pfizer’s 2009 Corporate Integrity Agreement was its third signed with the US government over its marketing practices, following agreements signed in 2002 and 2004 False Claims Act cases. Often such an agreement will mandate accountability for various compliance outcomes to a compliance director who will report to the CEO rather than to the general counsel. We believe these Corporate Integrity Agreements can be reformed to be much tougher in terms of the consequences for their breach and more demanding in terms of obligations to report on compliance on the internet. In this way agreements can be rendered much more effective than they currently are.\textsuperscript{21}

The initiative for False Claims Act cases normally comes from whistleblowers within a corporation that is alleged to have perpetrated fraud against the government. In other cases, such as the Lilly case above, the whistleblowers have been more junior sales representatives. The whistleblower goes to a law firm that specializes in \textit{qui tam} suits. Young Barack Obama was one of the lawyers representing Dr Janet Chandler, who won an international whistleblower award for her courageous 18-year struggle on behalf of her patients in an early False Claims Act case against Cook County Hospital for forging data and failing to comply with federal human research regulations.\textsuperscript{22} The case ended in a Supreme Court victory. Dr Chandler today leads a mentoring network of Taxpayers Against Fraud and the International Association of Whistleblowers, which supports whistleblowers during their new struggles.


\textsuperscript{21} For proposals for reform to make Corporate Integrity Agreements more effective and accountable, see Ford C and D Hess (2011), ‘Corporate monitorships and new governance regulation: in theory, in practice, and in context’, \textit{Law & Policy}, \textbf{33}(4), 509–41.

President Obama has sought to strengthen and clarify the False Claims Act in ways that should further increase the flow of suits; his measures include the Fraud Enforcement and Recovery Act of 2009 and the Patient Protection and Affordable Care Act, 2010. *Qui tam* fraud recoveries more than quadrupled between 2008 and 2012.23

10.4 HOW THE FALSE CLAIMS ACT WORKS

It is important to note that whistleblowers, non-governmental organizations (NGOs) and others who launch *qui tam* suits are not required to have been harmed by the defendant’s conduct in any way. This is not private law to recover personal losses as in tort; it is a private right to enforce public law encouraged by a reward for doing so. Whistleblowers and other plaintiffs file lawsuits “under seal”, so that they are concealed from the public and the defendant until the government has time to decide if it wants to join the lawsuit. The state can decide to run the case criminally, civilly or both. As can be seen in the list above, with big pharma cases it is usually both. If the state then runs the case successfully on the basis of information in the initial filing, the whistleblower gets at least 15 per cent of what the state recovers in the suit, with the court having discretion to award to the whistleblower up to 25 per cent of the amount the government recovers. If the government decides not to join the lawsuit, the plaintiff who wins on his or her own gets a guaranteed 25 per cent and up to 30 per cent (the government still receives the rest). They must pay their lawyers out of this.

*Qui tam* is therefore a solution to the problem that whistleblowers tend to be permanently tainted as employees. Once they have blown the whistle, they find that their career within the firm disintegrates.24 If their competence is in supply of pharmaceuticals to hospitals, they find that other pharmaceuticals contractors will not hire a whistleblower. One survey of 90 whistleblowers found 54 per cent saying they were harassed at work; 82 per cent reported harassment by superiors, 80 per cent physical deterioration and 86 per cent “negative emotional consequences, including feelings of depression, powerlessness, isolation, anxiety and


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Another study of 233 whistleblowers by Donald Soeken of St Elizabeth's Hospital in Washington, DC, found that 90 per cent were fired or demoted, 27 per cent faced lawsuits, 26 per cent sought psychiatric or physical care, 25 per cent experienced alcohol abuse, 17 per cent lost their homes, 10 per cent attempted suicide, and 8 per cent were bankrupted. Qui tam provides a financial incentive for whistleblowers to put up with all this in cases where the government has been defrauded of large sums. If, as a result of the qui tam suit, the government takes action and recovers $30 million from a pharmaceutical manufacturer, the whistleblower's share will range from $3 to $6 million. This might be sufficient to start a small business or to invest for a comfortable retirement after paying lawyers’ fees. It can provide sufficient incentive for employees to blow the whistle in organizations that commit large frauds. The bigger the fraud and the deeper the pockets of the fraudster, the more economically remunerative qui tam is for whistleblowers. Big pharma fears qui tam because the sector is big and its frauds are big. They are bigger than the combined cost of most kinds of property crimes that preoccupy criminologists.

American qui tam since the 1986 reform has proved less rife with abuse than its precursors because the whistleblower against an alleged fraud must first give the Department of Justice a chance to join or effectively take over the action. One cannot however conclude that it has been entirely free of vexatious claims. Justice decides to take on most of the meritorious False Claims Act actions because if the case is meritorious and Justice declines to take it over, the whistleblower’s legal team can still take a private action and win twice as large a percentage of the recovered false claims, leaving the revenue poorer and the Justice Department embarrassed by its error of judgement. On the other hand, counsel for a whistleblower with a less meritorious case will advise


caution if Justice declines to adopt the suit. In that situation, they will bear all the enforcement costs and risks and find themselves facing a judge who knows that this is a *qui tam* case found wanting by the Department of Justice. The ingenious private-public hybridity of the False Claims Act is that talented private lawyers and private investigators add value to public enforcement efforts. Yet the objective of the False Claims Act bar is always to improve their chances of a broad-ranging payout by persuading Justice to join with them and add what they know to the case. As the *Economist* puts it: "Some corporate executives squeal that the new rules [extending *qui tam* in US corporate law] will produce waves of frivolous claims by gold-diggers. But the evidence so far suggests that the quality of tips has gone up, not down".  

Advocates of *qui tam* before the 1986 amendments to the False Claims Act had a wider vision of the arenas in which *qui tam* might apply. They wanted it to cover major crimes against consumers, workers and the environment in addition to financial fraud against the government. They foresaw consumer groups working with whistleblowers to lodge sealed complaints that would give the Food and Drug Administration or the Federal Trade Commission an opportunity to join in major antitrust or consumer protection cases. This would have meant *qui tam* being available not just for instances of financial frauds perpetrated by pharmaceutical companies, but also for fraud in the testing of drugs, unsafe manufacturing practices, occupational health and safety and environmental offences, misleading marketing, bribery and antitrust offences, and indeed all the problems addressed in Parts I and II of this book. This generalizing of *qui tam* beyond false claims to all forms of corporate crime is what we advocate in this book. In an unsafe manufacturing practices or counterfeiting case, for example, this would mean that the whistleblower could simply claim a percentage of a large fine. In the United States in recent years some broadening of the policy of sharing fines with whistleblowers has begun to occur – to foreign bribery, securities and tax offences, and some environmental offences. The pre-1986 *qui tam* literature also prescribed some of the checks and balances that could be deployed for state lawyers to supervise private *qui*

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tam and to craft laws ensuring that *qui tam* actions could be dismissed by courts where suits compromised the integrity of a publicly articulated enforcement policy.

If penalties were high enough (see the discussion of equity fines below), there would be enormous potential for a law that enabled *qui tam* to operate where unsafe manufacturing practices led to the distribution of contaminated drugs. The same would apply if there were very high penalties for fabrication and fraud in testing the safety and efficacy of drugs. Experience across the decades demonstrates how many ethical people with high professional standards work for pharmaceutical companies. Such professionals often become disillusioned at the behaviour of their firm. Consumer groups and professional associations have a role here in encouraging whistleblowers to defend public health by launching a *qui tam* action. One of the possibilities for *qui tam* is that an organization like Healthy Skepticism, which organizes doctors to write to pharmaceutical companies in large numbers complaining of a specific example of unethical marketing, could launch a *qui tam* action that, if successful, could fund their further advocacy work. Some advocacy groups might collaborate with a law firm to become specialists in running *qui tam* actions against pharmaceutical companies. Trade unions could support strategic occupational health and safety *qui tam* actions in the way that Taxpayers Against Fraud currently supports whistleblowers in False Claims *qui tam*. In the United States there are public interest law firms that pay the living expenses of whistleblowers during the long years of unemployment that can haunt them between going public and winning a False Claims suit.

One check that could be put in place here would be a stop on *qui tam* in circumstances where a medicines regulator was already taking enforcement action against the company at any lower level of its enforcement pyramid (see Chapter 8) before the *qui tam* action was lodged. This stop should apply even if the enforcement action were only at the level of a restorative justice conference that led to a settlement ratified by a court. One virtue of such a law would be that it would encourage firms to disclose to the regulator abuses detected by their internal compliance systems and to ask the regulator to initiate a restorative justice process that would protect the firm against the possibility of *qui tam* initiated by a whistleblower. In circumstances where a *qui tam* suit launched by Healthy Skepticism was feared by the company, the regulator would hopefully invite Healthy Skepticism into the restorative justice circle. In some such cases the firm might be required to pay Healthy Skepticism's costs as part of the agreement. *Qui tam* in this way could become another force pushing enforcement action down to the
more efficient and effective base of the enforcement pyramid (see Chapter 8).

Already the design of the False Claims Act in the US, especially as revised in 2009 and 2010, creates serious incentives for firms to have credible internal compliance systems, and to report to the Department of Justice any fraud against the government detected by those systems and to persuade Justice that they have put in place a compliance plan to prevent future fraud. By reporting, the company reduces its damages liability from treble to double damages and eliminates penalties that can be imposed under the Act beyond the damages. Corporations rarely allow False Claims Act cases to go to court, preferring in the overwhelming majority of cases to settle.

If regulators sit on their hands and do nothing about a major crime in the pharmaceutical industry, consumer groups, whistleblowers and the *qui tam* bar can collaborate in persuading regulators to be more fearless in doing their job. This is the greatest potential strength of *qui tam* extended to all types of corporate crime in the pharmaceutical industry. There are plenty of regulatory officials who would be happy if they were forced by *qui tam* suits to show the backbone they feel they should be displaying. It could overcome their fear that their political masters will not thank them for showing backbone (see Chapter 8). Even in a world where politicians, and therefore in some instances regulators, are captured by political campaign contributions from big pharma, a bold extension to the 1986 False Claims Act reforms, extending the scope of the Act to cover all the crimes of the pharmaceutical industry, could work. It would surely mean that even the largest of campaign donations would not save a corporation involved in criminal activities from the networked private enforcement of NGOs, whistleblowers and a specialist public interest bar armed with *qui tam*.

Criminal firms sometimes worry about competitors attacking them through a *qui tam* action. Personnel often move from one company to its competitors, sometimes because they are troubled by the ethics of the company for which they used to work. This is one factor in competitors being the second most common initiators of False Claims Act suits in the United States after internal whistleblowers, as illustrated by the 1997 SmithKline Beecham case listed above. The industry grapevine is another factor. Any insider who has personally been involved in perpetrating a fraud will be prohibited from receiving a False Claims payout relating to the matter. However, such an insider can be approached by a competitor, who suspects the fraud and resents the competitive advantage it confers, to move to the competitor's employment and be rewarded for assisting his new employers in organizing a suit against the criminal firm.
Pamela Bucy sees genius in the “dual-plaintiff design” of the False Claims Act that provides both for collaboration between private and public regulators and for mutual checking and balancing of each other’s mistakes and abuses.30 Defendants’ reputations are protected, while allegations are kept under seal and the interpretation of the acts or omissions in question by public law enforcers competes with that by private law enforcers. This makes for a more circumspect approach than in tort litigation. Tort litigants have an untrammelled incentive to maximize their reputational assault in order to induce a quick and favourable settlement. More than that, the dual-plaintiff design of post-1986 qui tam “provides a structured way for private justice litigants and regulators to maintain a dialog about regulatory policy, and for regulators to provide case-specific guidance and oversight of private litigants”.31

Qui tam does not clog the courts with minor cases. It can clog the Justice Department with a huge backlog of major cases against big pharma, as seems to be the case at the time of writing. Specialized False Claims Act lawyers and whistleblowers do not risk litigation in cases where the anticipated recovery would not amount to a large sum. This is not to say that qui tam entirely avoids the risk of over-enforcement, uncertainty and disruption to the lives of the innocent, nor that it has been without abuse.32 Prudent judicial custodians of the institution need to be watchful. The legislature must also stand ready to fine-tune the level of qui tam payouts and regulate contingency fees. Empirically, if over-enforcement becomes a large problem, the first response should be to reduce the statutory percentage of the payout received by plaintiffs, not to repeal the law.33 Moreover, policy learning and adjustments can be made to the manner in which oversight of qui tam by the Department of Justice and by the courts is ensured. Bucy makes a strong case that the current design of qui tam under the False Claims Act brings with it only

31 Ibid., p. 69.
33 The implicit normative position here is that there is nothing inherently wrong with legislating for contingency fees to be shared between whistleblowers and their lawyers. John Braithwaite has argued that contingent remuneration of tax practitioners on the basis of the reduction in tax liability they secure for their client should be banned. That was because those tax contingency fees engender a market in vice. The argument in this chapter is that qui tam contingencies create a market in virtue. Law should therefore be designed specifically to allow those contingencies, including for tax enforcement. See Braithwaite J (2005), Markets in Vice, Markets in Virtue, New York: Oxford University Press.
a small risk of over-enforcement as compared with its considerable potential to remedy rampant under-enforcement.\textsuperscript{34}

It is instructive to ponder why, if it was so easy for whistleblowers to force pharmaceutical companies that had defrauded the US government to pay billions of dollars in fines, the government previously did not litigate to collect its money before the advent of \textit{qui tam}. One reason is the political capture of the state by big pharma. Another is reflected in Pamela Bucy's conclusion regarding the special power of private enforcement to mobilize two things that public enforcement fails to elicit: inside information and entrepreneurial legal talent.\textsuperscript{35} We have seen that \textit{qui tam} provides the incentive for insiders to blow the whistle. That sort of incentive is lacking when we simply provide a right for citizens to initiate actions under a public regulatory law, or provide for class actions.

Even so, it remains the case that private tort actions have hammered pharmaceutical companies much more than have publicly initiated prosecutions. Private actions have also brought into the public arena much more information about corporate crime in the pharmaceutical industry than have public prosecutions.\textsuperscript{36} \textit{Qui tam} has now demonstrated that in instances of fraud against the government it can achieve more than tort litigation launched by private legal entrepreneurs on behalf of victims. This is because victims are not well informed about breaches of law by the company. Only insiders possess that knowledge. The victim knows only that her body has been broken. Often it will be hard for her to pin the blame for that onto the company. The company can argue that the plaintiff was a sick and vulnerable patient to start with, which is why she took the drug. It can also argue that it never claimed that consuming the drug was free of risks. In fact it disclosed a wide variety of risks in the product information sheet provided to doctor and patient. The company can further argue that on average benefits exceed risks, even though in the case of this particular patient those risks were unfortunately encountered. Or it can parry that there could have been adverse interactions with another company's drugs which were not prescribed appropriately. Perhaps the patient had not taken the recommended dosage on exactly the recommended schedule, or perhaps she took it with alcohol when this was explicitly warned against. All these are reasons why tort cases are extremely inefficient, with most of the dollars spent on them landing in lawyers' pockets. With False Claims Act cases, in contrast,

\textsuperscript{34} Bucy, 'Private justice', op. cit.
\textsuperscript{35} Ibid., p. 43.
most of the dollars go to the public revenue, with whistleblowers and their lawyers also doing quite well. There is an argument, of course, that the returns should be earmarked for victims or for strengthening the capabilities of the relevant regulatory body.

It is hard to win tort cases without uncovering inside evidence of corporate negligence. This is the reason for the paradox that winning is harder in tort cases than it is by proving in False Claims Act cases, with the support of insider evidence, that there has been criminal fraud beyond reasonable doubt. \textit{Qui tam}, expanded in the ways proposed by Pamela Bucy\textsuperscript{37} and Brent Fisse,\textsuperscript{38} could therefore result in many criminal convictions of pharmaceutical companies across the entire gamut of crimes covered in the chapters of this book. The important thing about the kind of \textit{qui tam} we advocate is not that punishment of corporate crime would be increased, rather that more insider evidence of crime would become public. The greatly enhanced risk of criminal enforcement would result in companies improving their internal compliance systems and reporting to the government regulator the serious crimes that they detect, requesting that a negotiated settlement be ratified by a court as an “enforceable undertaking” or a Corporate Integrity Agreement. This at least is what would happen if the law prevented \textit{qui tam} from proceeding in instances where the government was already taking action against the company for the crime, with that action to be ratified by a court.\textsuperscript{39} In other words, the primary benefit of well-crafted \textit{qui tam} would be preventive prior to enforcement rather than deterrent after enforcement, though there would be deterrent benefits as well.

The idea of the False Claims Act has not spread beyond the United States. Reform debates on \textit{qui tam} are currently under way in the European Union, Russia and Australia, though we are not aware of a country where they have yet progressed far.


\textsuperscript{38} Fisse and Braithwaite, \textit{The Impact of Publicity on Corporate Offenders}, op. cit., pp. 251-4.

\textsuperscript{39} Parker, ‘Restorative justice in business regulation?’, op. cit.
10.5 OPENING INTERNET REPORTING TO PRIVATE ENFORCEMENT ENTREPRENEURS

Pamela Bucy’s most fundamental insight is that the “more complex and interconnected our world, the more essential inside information becomes to effective regulatory efforts”.40 If public reporting of inside information is improved, advocacy groups and qui tam law firms can more effectively draw out insiders who know where the bodies are buried. This is one reason why a number of corporate tax experts41 have argued for an appropriate form of disclosure on a public website of the key information in corporate tax returns so that the entrepreneurial talents of private forensic accountants might be deployed to find frauds that tax authorities miss in complex accounts. Their reward for finding them should be a share of the tax recovered. This would be particularly useful for corporate crime in the pharmaceutical industry since pharmaceutical companies are among the most accomplished tax evaders, for example shifting profits into tax havens. So-called “sunshine laws” that require disclosure of gifts and other “transfers of value” to doctors and health professionals by pharmaceutical companies is another good practice.

Crimes against human health could also be prevented by laws that require the results of both Good Manufacturing Practices (GMP) and Good Laboratory Practices (GLP) regulatory inspections and internal compliance reports to be placed on a public website. The worry about such a law is naturally that internal compliance auditors would write less frank audit reports when they know that these will be made public. The remedy for this is to grant the company immunity from criminal prosecution so long as it discloses the crime, compensates victims, suitably disciplines all the individuals responsible (for example by dismissal, demotion or withholding a bonus) and puts in place new procedures to prevent recurrence. These must be evaluated independently as effective.42 All this must be done through a set of written enforceable

40 Bucy, ‘Private justice’, op cit., p. 79.
42 Jurisprudentially, Brent Fisse argues that this justifies a rethinking of corporate criminal law to prioritize reactive fault over the current backward-looking and causal theory of fault in western criminal law. See Fisse B (1983),
undertakings that are also publicly disclosed and ratified by a court as a suitable response.\footnote{Reconstructing corporate criminal law: deterrence, retribution, fault and sanctions, \textit{Southern California Law Review}, 56, 1141. John Braithwaite has given a republican defence of a radical reconfiguration of western criminal law so that it gives more priority to forward-looking active responsibility, as compared with Fisse’s concept of reactive fault, and becomes in practice more akin to some Asian criminal law. See Braithwaite J (2001), ‘Intention versus reactive fault’, in Ngaire Naffine, Rosemary Owens and John Williams (eds.), \textit{Intention in Law and Philosophy}, Aldershot, UK and Burlington, VT: Ashgate, available at http://www.anu.edu.au/fellows/jbraithwaite/_documents/Chapters/Intention_Versus_2001.pdf.} Only if the company implements remedies that are unsatisfactory on one of these fronts would the court be able to allow a criminal prosecution. The paradox, we suspect, is that such a policy would mean that advocacy groups and \textit{qui tam} law firms would obtain good leads as to where more bodies might be buried. A company that has a disaster that it cannot cover up, and that it therefore discloses publicly in an internal compliance report, will often have other disasters that it believes it can cover up and has not publicly disclosed. External advocates for safer drugs can therefore establish contact with socially responsible insiders (who they might persuade to become whistle-blowers). Or advocates can reach out to other insiders who might connect the dots to detect a disaster that has been covered up after they see on a public website the full disclosure of another drug safety disaster within the firm.

We therefore consider that well-designed \textit{qui tam} can animate two paradoxes. The first is that criminal convictions for corporate crime in the pharmaceutical industry could become easier to achieve than victories in tort cases. The second is that immunity for public disclosure of corporate crime, combined with remedial plans approved by a court, could result in more rather than fewer convictions for corporate crime in the pharmaceutical industry than we have at the moment.

We consider that an important element in this aspect of our reform programme would be the nurturing of a tradition of compliance professionalism that is already maturing within the pharmaceutical industry. Up to the present, however, pharmaceuticals compliance professionals have quite often been subject to capture by the corporations that feed them. We therefore need a regulatory design that will expose slipshod compliance professionals. One can readily envisage how a system mandated by law that requires open internet reporting of both internal and government

\footnote{See Parker, ‘Restorative justice in business regulation’, op. cit.}
inspection reports would foster the maturation of independent compliance professionalism as a force for continuous improvement in the following way. An independent compliance auditing firm will monitor internal compliance reports on matters such as GMP and GLP in a company that it is interested in helping. If it detects certain weaknesses in a corporate system, the auditor can contact the company, pointing out that it has some good strategies to eliminate these shortcomings. The company may spurn the proposition of a new consultancy contract, but if it does so, it should be careful to solve the problem itself lest the spurned contractor drops comments to friends in the regulatory agency about the poor quality of the firm’s compliance work. If and when the company does run into trouble with the regulator, as revealed in the public disclosure of the regulator’s inspection, the compliance auditor might approach the embattled firm at that point with its ideas for a continuous improvement plan that will get the regulator off its back. Again, if the firm spurns this advice and hires instead a slipshod compliance auditor who produces a non-credible conclusion that the problem has gone away, an aggressively competitive compliance auditor has the option of telling either the firm or the regulator why its competitor’s report is slipshod. All these things that it can do to enhance its position in a competitive market for excellence in compliance auditing are only possible if publishing of compliance reports in considerable detail on the internet is mandated.

Perhaps the most critical rule of all in a regime of greater transparency would require companies to publish on the internet all raw data used in support of a new drug application. This would be self-enforcing under the kind of reforms that we propose, since any scientist suspecting that data which he or she has developed have been suppressed could go to the public website to check whether these suspicions are correct. If the data were indeed missing, the scientist could find it rewarding to launch a qui tam suit against the company. The very point of all the data being there is that other scientists might re-analyse it with greater integrity than the company. If the dishonesty of the company passes the threshold into fraud, the scientist will have the opportunity to publish the entire story and to obtain a rewarding qui tam settlement.

The pharmaceutical industry naturally argues that such safety testing data constitutes a commercially valuable asset that must be dealt with in confidence. Similar arguments regarding trade secrecy were raised when governments after the thalidomide disaster first required the industry to make details of their research available to them to be shared with regulators from other countries. Now, as then, the public interest in drug safety should weigh more heavily than private interests in trade secrecy. One can no doubt validly argue that making information publicly
available on how to synthesize a new drug can discourage investment in innovation; however, requiring the disclosure of data on the safety of a drug, in the period preceding its sale to the public and thereafter, involves no such disincentive to innovation. It does, on the other hand, constitute a powerful disincentive to fraud. Our transparency proposal is radical, but the tide of history is slowly moving in this direction, especially in Europe.\textsuperscript{44} A century from now it will be viewed as odd that full transparency for research on the safety and efficacy of medicines was once a radical proposal.

10.6 EQUITY FINES

One of the worries about \textit{qui tam} is that it could increase reliance on fining corporations. There are a number of practical limitations of fines as sentences in corporate crime cases;\textsuperscript{45} we will focus here on the limitation that they can hit the wrong targets. If fines are sufficient to actually deter a large corporation, they may be so heavy as to cause the firm to lay off workers and threaten the communities that depend on the company’s workforce for their survival. With a pharmaceutical company that must sustain spending on a range of matters critical to public health, there is a concern that a large fine might in effect be funded by reducing R&D on new drugs or orphan drugs or cutting corners on drug safety or on post-marketing surveillance. With firms enjoying significant monopoly power, the greatest fear is that they will simply pass on the punishment to consumers in higher prices, meaning that some poorer consumers may no longer be able to afford the drugs that they produce.

One solution to this problem, at least in the home country of a pharmaceutical company, is John C Coffee’s idea of the equity fine.\textsuperscript{46} Instead of a fine being calculated in dollars, it is calculated as a percentage of the market value of a company on the stock market. If an equity fine of 1 per cent is imposed, new shares amounting to 1 per cent of all shares in the company are issued. These newly issued securities are paid as the penalty. The effect of an equity fine is not to reduce the capital available to the company to invest in good things like R&D on new medicines. Rather it is to dilute the ownership of that capital. The


\textsuperscript{45} See: Fisse and Braithwaite, \textit{Corporations, Crime and Accountability}, op. cit.

\textsuperscript{46} Coffee, “‘No soul to damn, no body to kick’”, op. cit., p. 413.
original shareholders who owned 100 per cent of the company before the 1 per cent equity fine was imposed now own 99 per cent. The effect on markets would be the same as any share issue; the value of the shares would fall by 1 per cent as a consequence of the 1 per cent equity fine.

To take an example: let us assume that the share of the equity in a company awarded by a court as an equity fine is a million shares valued at $100 each. If the judge rules that the whistleblowers who initiated a qui tam action should be awarded 25 per cent of the equity fine, they would receive 250,000 shares with a total market value of $25 million. The government would receive 750,000 shares, which it could put into a victim compensation endowment or simply sell and contribute the proceeds to the revenue. If the state has a sovereign future fund for unborn generations, the shares can go there.

An advantage of the equity fine is that it takes the pressure off sentencing judges who are concerned that a large cash fine will be passed on and ultimately harm the innocent. With this pressure removed, judges are free to impose heavier fines that are a more credible deterrent and can provide insiders with more enticing incentives to blow the whistle. A private member’s bill in the Scottish parliament to legislate for equity fines was motivated in part by Lord Brodie’s comments in passing sentence on ICL Stockline for an occupational health and safety crime that killed nine people, causing community outrage: \(^47\)

There is then to be taken into account the ability of the companies to pay a fine and yet remain in business and provide employment.

The fines handed down in court often do not reflect the financial gain a firm may have made by failing to comply with an obligation. This means that these penalties do not act as a deterrent and, in effect, give businesses an incentive to continue to fail to comply in return for a profit. In some cases fines do not fully reflect the harm done to society.

While firms like Pfizer might be too big to fail and too important to nail, others might be too fragile to nail. Coffee alerts us to the fact that cash fines can put the sentencing judge in a “deterrence trap”. If the risk of detection for a corporate crime is one in fifty and the crime profits the company $200 million, then the prospect of any fine less than $10,000

million will make it rational to break the law. Fines set higher than $10 billion may push even large firms towards bankruptcy. Symbolically, access to the option of an equity fine, even if such fines are rarely imposed, would be a way of signalling to business that there are no circumstances in which it is impossible to escalate to a credible deterrent through "capital punishment" at the higher reaches of an enforcement pyramid (see Chapter 8). You are never too big to fail or too big to nail.

10.7 CORPORATE CRIME ENFORCEMENT IN DEVELOPING ECONOMIES

A fair summary of the literature that we have considered in Part II is that the worst corporate crimes in the pharmaceutical industry have occurred in developing countries. We have seen that many of these crimes have been committed by corporations with very deep pockets. In a poor country, where would the entrepreneurial legal talent be found to make a reform like *qui tam* work against powerful multinationals? The answer, surely, is that initially it would come from international NGOs, which, if they are good capacity-builders, will then train local lawyers working beside them to take over from them. International NGOs like Avocats sans Frontières, working with development agencies like the World Bank that support legal capacity-building, could also help in applying and adapting the lessons of English and American history regarding *qui tam*. These NGOs have an international intelligence network of sorts, meaning that if a pharmaceutical company were found to be using people in one developing country as guinea pigs to test a new drug in a reckless manner, the NGO would turn over the rocks to see if this was happening in other developing countries where the company was well established. This worldwide intelligence capability is not a new phenomenon; 30 years ago the international consumer movement established Consumer Interpol to distribute lists of products banned as unsafe in one country to check whether they were being dumped in another. In Australia, the Country Women's Association used its membership of more than a million women in all corners of the country to check retail outlets in order to determine whether products banned elsewhere had been dumped in Australia.\(^\text{48}\)

\(^{48}\) John Braithwaite was responsible for organizing this in the 1980s through the Australian Federation of Consumer Organizations of which the Country Women's Association was a member.
Today, the capability for public prosecutorial and civil justice oversight in developing countries is in fact not as weak as it was in the office of Abraham Lincoln’s Attorney-General. Legal governance in Lincoln’s day did not enjoy legal governance capacity-building support from private and public foreign donors, such as could well be mobilized to monitor abuse of *qui tam* in contemporary developing economies. Hence, *qui tam* laws of broad application to corporate crime in the pharmaceutical industry could be one of the more effective instruments that developing countries could develop to protect their citizens from crime. One must also realize that some developing societies, such as India, are strong democratic states with substantial, sophisticated bureaucracies and courts.

Across the globe today it still may be true that where state capacity is weakest, the case for reliance on *qui tam* is strongest. Conversely, where state regulatory capacity is strong, the need for private prosecution to fill gaps left open, because of the inadequacy of public enforcement, is less critical. Against this background, one might expect to find that in the situation pertaining in the United States today, where public enforcement is strong, *qui tam* would provide little in the way of added value. The fact that it clearly has added value to enforcement in the pharmaceutical sector in America may justify the hope that *qui tam* will prove even more valuable in weak states where opportunities to substitute for failed state enforcement are more plentiful.

If on the other hand the court system and justice bureaucracy in a developing country are themselves so inefficient or corrupt that they cannot cope with surges of *qui tam* actions, then these greater opportunities may simply not be practically available. Even in such circumstances, a strategy that can rely on private resources to do much of the justice bureaucracy’s work for it has better prospects than reliance on a wholly public process. Cooter and Garoupa show that one of the attractive features of bounties (combined with immunities for any minor roles that a whistleblower may have played in the crime) is that they can create conditions in which criminals are unable to trust each other. Corruption unravels when each partner in a crime is also a potential bounty hunter. An important feature of *qui tam* here is that only the first to lodge the

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*Qui tam* suit can collect the bounty. Hence there are disincentives among those with incriminating knowledge to sit back and hope that the problem will go away. There are incentives to be the first to turn to the prosecutor with that knowledge. Both the corrupt regulator who takes bribes and the executive who pays them are vulnerable to this incentive to be the "first in time" to the public prosecutor. Under pressure from the 2011 Dodd-Frank extension of bounty payments to securities law whistleblowers, some US companies are beginning to discuss internal corporate bounties for employees to report their concerns internally before approaching regulators.\(^{51}\)

International networking between lawyers who specialize in *qui tam* actions against multinational companies could be important. Cases relating to criminal acts in a country where the court system is weak could better be brought in foreign courts by members of the network practising there. While it is not likely that False Claims statutes to compensate developing states could be enforced in western courts, past experience in tort cases, such as those relating to the Bhopal chemical pollution disaster in India and the litigation brought by villagers in Papua New Guinea against BHP (now BHP-Billiton) over the destruction of their livelihoods by the pollution of the Fly River, has shown that globally networked law firms can have major impacts on multinationals. Where there is extraterritorial application of national laws, such as now exists in most western nations with respect to the payment of bribes to foreign governments, extension of *qui tam* to cover bribery could result in successful *qui tam* actions in western courts for bribery by pharmaceutical companies in developing countries. Were equity fines also available as a sanction under the US Foreign Corrupt Practices Act, for example, the possibility would be created of diverting some of the equity in a criminal American corporation from Wall Street to compensate victims of its corrupt conduct in a developing country.

Whatever the deficiencies of governance in developing societies, in an era of networked governance, weaker actors, if they are clever, can enrol stronger ones to support their projects. Anne-Marie Slaughter's work suggests that the globe is strewn with disaggregated bits of strong states that might be enrolled by weaker ones (and by weak NGOs).\(^{52}\) The drug regulator of a developing country can today enrol the support of the US Food and Drug Administration to audit the safety of unsafe clinical trials on a new drug being conducted on its population. NGOs in developing

\(^{51}\) Valencia, 'Year of the Bounty Hunter', op. cit.

nations may be weak, but they are becoming stronger both in their own right and in their capacity to enrol northern NGOs and international regulatory organizations into projects in order to compensate for the weak regulatory capacity in their home base. Responsive escalation up a regulatory pyramid can hence be accomplished not only by escalating state intervention, but also, as Peter Drahos has suggested, by escalating the networking of new tentacles of domestic and transnational governance (see Figure 10.1).53

Figure 10.1 A pyramid of networked escalation

The core idea of responsive regulation as a strategy actually has special salience for resource-poor states. This is the idea that no regulator has the resources to enforce the law consistently across the board and that limited enforcement resources therefore need to be focused at the peak of an enforcement pyramid. Networking escalation is an interesting demonstration of how to make the most of limited regulatory capacity. *Qui tam* is a statutory private justice reform that, instead of substituting public with private justice, institutionalizes collaborative networking that enables more credible regulatory escalation. Mobilizing public virtue to

regulate private vice is not the only path around capacity deficits. Private markets in virtue can also be mobilized to regulate vice, and indeed to flip markets in vice to markets in virtue. Where state capacity is weakest, both *qui tam* and responsive escalation via networking with progressively greater numbers of private and public enforcers should pay the highest dividends. Moreover, the networking of regulatory partnerships also structurally reduces the rewards of capture and corruption in those developing economies that are endemically prone to corruption.

One potential risk of responsive regulation results from the fact that it places more discretion in the hands of regulatory bureaucrats; if the latter are dishonest, they may then misuse that discretion to increase the returns to corruption. Here again networking can provide a check: the strategies of networking around state incapacity and mobilizing private markets for enforcing virtue have the attractive feature of exposing and preventing regulatory corruption. The private prosecution of a pharmaceutical company in the United States under the Foreign Corrupt Practices Act for bribing a health minister in a developing country would expose that health minister to diplomatic pressure from the United States, to domestic victims pursuing compensation in the United States, and to the international and national media.

There is a civic republican ideal in play here that is developed in Philip Pettit's work on republican political theory. Yet one does not have to be a Pettit style of social democratic republican to embrace the policy ideas. This ideal is for the attainment of a world in which public prosecutors, private markets for lawyering, and courts can together help whistleblowers to escape the domination of business criminals. Equally, courts and private *qui tam* litigants can join hands to defeat the joint domination of business criminals and of an executive branch captured or corrupted by them. Yet the same institutional design also allows for the joining of the separated powers of the court and the public prosecutor to protect an innocent business from a vexatious whistleblower. It is a somewhat messy ideal of cross-cutting deliberation of public reason. One must realize however that the best ideals are prone to be somewhat messy and redundant. They have to be because domination can come from so many unexpected directions.

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10.8 SCAPEGOATS AND SINNERS

One cannot pretend that all of the whistleblowers in the pharmaceutical industry have themselves been without blemish. Sometimes sinners seek to purify their reputation by casting the first stone. Accountability for the crimes of the drug industry has always been a sordid business, as it was in those companies where, 34 years ago, the authors first encountered “vice-presidents responsible for going to jail”. While individual accountability for corporate crimes seems like a laudable ideal, the reality that our research has revealed over the past four decades is the existence of smokescreens of diffused accountability that often allow only convenient scapegoats to be charged. Pharmaceutical companies commonly attempt to set up as their scapegoats the very whistleblowers who act in the public interest. Corporations may themselves promote the notion of individual accountability so that they can impugn “rogue individuals”, seeking to mask in this way the fact that the real problem is the existence of a systemically criminal corporate culture.

We have also seen in this chapter how pharmaceutical giants can sometimes make a case that they are too big to nail. One can readily sense how morally fraught the criminal prosecutor’s job can be in such circumstances. With drug crime, we believe the fundamental responsibility of prosecutors should be to prevent further loss of life. Potent sanctions like putting government administrators in charge of licensed pharmaceutical companies (Chapter 8) and the use of *qui tam* and equity fines (this chapter), should be imposed sufficiently often to motivate cooperation by firms with a restorative justice approach to corporate crime in the industry. This means that when a corporation walks into a regulator’s office to confess to a crime out of fear of such robust enforcement, then restorative justice can be the best way to prevent crime and to save lives. This will only be true, however, if internal disciplinary measures of formidable comprehensiveness are put in place, and provided Corporate Integrity Agreements of sweeping effectiveness, and with real teeth to ensure public enforcement in the event of breach, are also promptly implemented.\(^{55}\) This is why it seems vitally important to protect firms from *qui tam* if they confess a breach to the regulator and reach a restorative justice agreement that can satisfy a judge as a creditable path to protecting the public health.

\(^{55}\) See Fisse and Braithwaite, *Corporations, Crime and Accountability*, op. cit.
Many readers will see this as a disproportionately soft response to serious crime. However, as argued in Chapter 8, a regulatory regime with high detection and enforcement rates, heavy reliance on learning from mistakes, and a generally low quantum of punishment (except when cover-up or recalcitrance make it necessary to escalate to the peak of the pyramid) can be a better way of using a sword of Damocles to protect public health. Even so, the sword of Damocles must be sharp. This is why we think that equity fines (even if rarely used), combined with whistleblower access to *qui tam* payouts for all serious regulatory crimes (not just false claims), can motivate restorative justice that produces Corporate Integrity Agreements of genuine ethical bite. The *qui tam* and equity fine reforms are particularly critical for the major drug-exporting states such as the United States, United Kingdom, France, Germany, Switzerland, Japan, Sweden and Denmark.

10.9 THE LURE OF THE LOOTER

Lure became a central concept for diagnosing corporate crime in Neal Shover and Andrew Hochstedler’s *Choosing White-Collar Crime*.56 One of the challenges advanced in the Maurice Punch book, *Dirty Business*,57 is his view that while corporate ethics, voluntary self-regulation, negotiated settlements and responsive regulation are all useful strategies, none of these things is useful in challenging domineering figures who take over large companies and loot them to support extravagant lifestyles for themselves and their families. By the mid-twentieth century, looting by “robber barons” was not a prominent phenomenon in the pharmaceutical industry. Perhaps this has been because profits have been so lucrative in the pharmaceutical sector that looting has a lower comparative advantage as a strategy for acquiring personal wealth. As profits fall for large sections of the pharmaceutical industry, however, this situation could change. Examples of looting by “robber barons” in other sectors therefore merit some attention when one considers the future.

Robert Maxwell is portrayed by Punch as a paradigm villain. From the 1960s to the 90s Maxwell looted Palgrave Publishing, the Daily Mirror group and various other companies that he had acquired while he was an

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influential public figure and a beacon of the British business establishment. Ultimately, with the exposure of his massive fraudulent dealings, Maxwell’s life ended in an apparent suicide.

BCCI (the Bank of Commerce and Credit International) was another instance of massive looting. Punch considers that this was facilitated by the bank being set up as an offshore entity in every country where it operated. Ultimately it was identified as a criminal business organization that was “executed” when the Bank of England closed it down. Such phenomena were not to remain unique: within the decade after the publication of Punch’s study, Conrad Black emerged as another media magnate of the Maxwell type who ended in prison.

Chapter 11 of the present volume considers one limited solution that might have been applied in a case such as that of BCCI. It involves the development of a more cosmopolitan philosophy among regulators and prosecutors that could have led to earlier intervention. Ultimately, however, a company that had been looted as extensively as BCCI was in any case likely to collapse. In such a situation the objective must be to truncate the duration of looting so that more remains for innocent depositors and investors. With a lot of luck, however, it might even be possible to secure a conviction sufficiently early to provide the basis for an equity fine or for a state regulated takeover as a going concern of an entire criminal empire, such as that of BCCI and Maxwell, with a new management to recover looted losses.

We suspect that where massive looting of a company by those in power emerges, a *qui tam* strategy is the best approach for accomplishing a rush to the prosecutor’s office to be the first to claim a slice of the penalty. Among those who can rush to the prosecutor are the director of a company that has been looted by its CEO. The director may do so to head off *qui tam* initiated by a whistleblower and to avoid prosecution for breach of directors’ duties. One reason for the late exposure of the extent of Maxwell’s looting was that for a long period everyone, including the most sophisticated observers of the British stock market, thought of Maxwell as a successful tycoon. In the early stages of his looting, potential whistleblowers would have thought Maxwell was merely stealing from massive businesses that still had plenty of resources left for him to loot. This naive belief had largely faded some decades later when the story ended with Maxwell disappearing over the side of his luxury yacht. Criminals like Maxwell get away with looting for a long time because they are individuals who are effective at cajoling or intimidating those who work for them, convincing them that the tycoon can destroy them should they turn on him. At the same time, even Maxwell was unable to skim so much money through tax havens for his personal benefit without
the assistance of many financially sophisticated insiders within his companies.\textsuperscript{58} That is why we think specialist \textit{qui tam} law firms can provide the needed support to the insider who chooses to blow the whistle early on a Maxwell. It can guarantee such an individual a financially secure future beyond the looter's reach.

Other remedies that Punch himself mentions can also help – more vigilant shareholders who have access to more transparent regulatory assessments (including those from ratings agencies, which we consider in the next chapter), more vigilant outside directors and outside auditors, public and private support for advocacy organizations to monitor and contest the policies and practices of the pharmaceutical industry, business ethics training in business and accounting schools that seek to contribute to more ethical business cultures, requiring business codes to be enforced rather than being mere pieces of paper, government regulators who take seriously their responsibilities as “guardian angels”,\textsuperscript{59} who get the “mug shots” of business criminals into the financial press to reinforce the message that crime is crime even when the criminal sits in the House of Lords, and a more vigilant media.

Traditions of investigative journalism are rarely profitable and are currently under threat. After Rupert Murdoch took over the \textit{Times} of London, the \textit{Sunday Times} insight team that had exposed the thalidomide scandal and the worst drug testing fraud in Australian history\textsuperscript{60} was shut down. Today James Murdoch is on the board of GlaxoSmithKline. In the next chapter we make a case for public broadcasters, like Britain’s BBC, to consolidate and develop a core of sound investigative journalism. All of these are admittedly thin reeds that have repeatedly snapped in the face of the power exerted by personalities such as Maxwell or the Murdochs, or in later years the leaders of Enron who were friends of the two Bush presidents in the United States. Yet even such thin reeds can

\textsuperscript{58} The chair of the Parliamentary Select Committee that investigated the Maxwell affair, said, among other things, “if insiders had been brave enough to resign and talk”, or if professional advisers, directors or bankers had cared more about their responsibilities and less about their fees, the whistle might have been blown early. Quoted in Punch, \textit{Dirty Business: Exploring Corporate Misconduct}, op. cit., p. 8.

\textsuperscript{59} Ibid., p. 251.

\textsuperscript{60} This was perpetrated by Professor Michael Briggs of Deakin University. Briggs fabricated data on products such as oral contraceptives in return for large payments from many major pharmaceutical corporations.
be woven together to form a better fabric of checks and balances\textsuperscript{61} of the abuses of robber barons, so that we can have fewer of them and demolish them earlier. No capitalist society can ever totally eradicate them, nor could any socialist society.

\textsuperscript{61} Weaving together thin reeds of state and non-state regulatory controls is a theme of Braithwaite J and P Drahos (2000), \textit{Global Business Regulation}, Cambridge: Cambridge University Press.
11. A new capitalism: A new drug diplomacy

11.1 OLD CRIMINOLOGY; OLD CAPITALISM

We have brought a criminological perspective to the study of the pharmaceutical industry. We do not, however, portray criminal law as a day-to-day driver of reform. Even a massive dose of criminal deterrence cannot begin to solve the problems of the pharmaceutical industry and its relationship to society. Rather we see criminal enforcement as having a role to play as a catalyst of transformation for the pharmaceutical industry in moments of crisis, national or global. As we have argued in Chapters 8 and 9, criminal enforcement can spark transformation provided that it is integrated into webs of networked escalation up pyramids of supports and sanctions.

Our final chapter moves that analysis up a notch. In it we introduce a broader view of the key supports for transformation that might be mobilized in moments of crisis affecting the pharmaceutical industry. First, we identify the players who have an interest in abandoning the old pattern of capitalism within the pharmaceutical industry in favour of new business models that can forge an innovative new capitalism. After considering the new venture capitalists of that new capitalism, we then consider who might be the diplomats of global drug diplomacy who can build political support for reform. Joseph Schumpeter argued that capitalist development is about "creative destruction" of old business models by new ones.¹ This chapter presents the view that crises of corporate crime in the pharmaceutical industry can in effect benefit that industry by helping to catalyse the "creative destruction" of an outdated capitalism that will fail the tests of the twenty-first century, especially in the emerging economies.

During the twentieth century, the big pharma business model was oriented towards making profits in wealthy countries: in western Europe,

North America and Japan with their high consumption of patented pharmaceuticals. The middle class in developing countries was a secondary market, though not such an important one in the twentieth century when those middle classes were small. Big pharma had some interest in developing countries as places where regulatory oversight was lax, allowing forms of drug testing and innovation in marketing that might invite lawsuits if undertaken in their home countries. Bribes were often paid to keep regulators on a leash (see Chapter 5). Big pharma also took a critical interest in pharmaceutical manufacturing in developing countries when the latter sought to become internationally competitive by promoting and exporting generic drugs in a manner that seemed to threaten the global intellectual property order.

As developing markets grew in the late twentieth century, big pharma's disjointed approach to these markets resulted in the emergence of a monster. That monster is a counterfeiting industry based in developing countries, but more importantly in China and India, and now presenting a vast and still expanding threat to global health (Chapter 5). In the rich countries, state regulators became capable of suppressing counterfeiting operations when patent owners drew the regulators' attention to them. No such capability existed given the enfeebled and benighted regulatory mechanisms that existed in most developing markets. With patented drugs unaffordable in developing countries and with competition from generics severely truncated by international trade diplomacy enforced by the United States and the European Union, a vast competitive opportunity opened up for counterfeiters as newly industrializing economies grew.

The BRIC countries - Brazil, Russia, India and China - have so far failed to respond to this catastrophe by leading a new trade diplomacy attuned to the interests of developing countries. India's recent initiative in establishing an open-source biotechnology project to conquer tuberculosis is a noble exception (see Chapter 8). Such a new diplomacy would promote a new world intellectual property order, favouring the challenge to patent monopolies provided by competition from generics, the production under compulsory licences of essential drugs for the poor and the development of open-source business models as alternatives to the deadly competition from counterfeiters. We return to this trade diplomacy theme in the second part of this chapter.

A current stream of thought in regulatory studies has it that the contemporary era of capitalism is not so much one of neoliberalism in which free markets prevail, but rather one of regulatory capitalism, where
both markets and regulation have become progressively stronger. The authoritarian capitalism of the Second World in China, Russia and its former satellites is not neoliberal. Since the global financial crisis struck in 2008, authoritarian Second World capitalism has been gaining credibility in Africa and across the remainder of the developing world. Firms that are either minority or majority state owned are dominant forces in post-2008 capitalism. We have seen how there was strong growth in pharmaceutical regulation in western economies following the thalidomide disaster. Unfortunately, there has been even stronger growth in intellectual property regulation crafted at the behest of the industry’s monopolists. This has been so vigorous as to defeat the maturation of the other leg of regulatory capitalism, namely increasingly vigorous competition in markets. All the same, we have seen that the competitive dynamics of regulatory capitalism have in a perverse way remained

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4 State ownership of the largest firms has grown in East and South East Asia since the late 1990s (Carney RW and TB Child (2013), ‘Changes to the ownership and control of East Asian corporations between 1996 and 2008’, *Journal of Financial Economics, 107*(2), 494–513). In 2005, none of the top ten on the Forbes biggest corporations list were publicly owned; in 2010, four were majority publicly owned: three Chinese, one Japanese (Mussachio A and S Lazzarini (2012), ‘Leviathan in business: varieties of state capitalism and their implications for economic performance’, SSRN Working Paper). By 2012 a majority publicly owned Brazilian company had joined the top ten and Russia’s Gazprom was not far behind at fifteenth.
robust. The effect of closing off legitimate competition with the industry’s monopolists has been that the burgeoning competition has come from criminals – counterfeiters who have found havens in authoritarian capitalist states.⁵

11.2 A MORE PRINCIPLED REGULATORY CAPITALISM

We must now seek to determine what sort of interventions in the dynamics of regulatory capitalism might save most lives. The first requirement is for a transfer of regulatory expertise so that the basic drug regulatory capabilities that have been in place in wealthy economies for decades develop similarly in developing economies with support from donors. One condition that must be attached to this aid is that it be accompanied by continuous strengthening of anti-corruption institutions. A combination of basic drug regulatory and anti-corruption capability can put an end to counterfeiting. This is admittedly more easily said than done, but it is entirely feasible, especially as developing countries continue to pool their expertise in regional systems. In those sectors where the West has had sufficient interest in improving the regulatory capabilities of developing countries (as with its need to protect its own tourists and business travellers by ensuring the safety of worldwide air travel), it has been able to transfer the capability of improving safety provisions at a pace comparable (or faster) to that achieved in western history. We also concluded in Chapter 10 that the availability of qui tam under western anti-corruption laws with extraterritorial application (such as the US Foreign Corrupt Practices Act) could assist greatly through the enforcement in western courts of measures to counter corruption in developing economies.

One kind of regulatory transfer that developing countries do not need is in the regulatory strategies of western patent offices. Assisting developing countries to establish patent offices following the model of the US and European patent offices is a widespread form of foreign aid that should be abandoned. Private foundations or innovative developing

⁵ This is an instance of Cloward and Ohlin’s elaboration of Robert K Merton’s criminological theory: crime flourishes when legitimate opportunities are closed and illegitimate opportunities are open. Cloward R and L Ohlin (1961), Delinquency and Opportunity: A Theory of Delinquent Gangs, Glencoe, IL: Free Press; Merton RK (1949), Social Theory and Social Structure, New York: Free Press.
economies like Brazil that have a history of rejecting western intellectual property doctrines might well show leadership in research to design a new architecture of patent office administration that jointly optimizes both invention and the diffusion of innovation to benefit the poor.\textsuperscript{6} While it is most unlikely that every developing nation could afford a patent office that weighs from first principles the public benefits and costs of each patent application for drugs that it evaluates, collaboration between the patent office administrations of a group of developing economies intent on reform would be entirely feasible. Each participating country might, for example, assume responsibility for making recommendations on patents for just one class of drugs. If other nations in the collaboration possessed one or two particularly distinguished experts on that class of drugs, these experts could be seconded to the patent office of the country taking responsibility for the class. The Eastern Carribean Drug Service is an incipient example of such collaboration.

Another radical reform option is to take patent administration for pharmaceuticals completely out of the hands of patent offices in developing economies and transfer drug patents to the pharmaceutical regulatory authority. Again, Brazil has shown how this can be done.\textsuperscript{7} One argument for this approach to reform is that pharmaceutical regulatory expertise is a scarce resource in all developing economies (and indeed in developed ones as well) so that it makes sense to avoid the fragmentation of that expertise among multiple regulatory agencies. We have already argued that compulsory licensing of pharmaceuticals should be an option in the regulatory pyramid where patent monopolists are foiling efforts to fight major epidemics such as HIV (Chapter 8). In a world where pharmaceutical regulators are also charged with making recommendations to their governments on compulsory licensing decisions, they will acquire added authority as regulators of intellectual property. Creating a one-stop-shop for pharmaceutical regulation of all kinds also makes sense in terms of administrative efficiency; the system could be crafted to reduce substantially the burden of paperwork weighing on business.

As argued in Chapter 8, a good way to move towards radically new institutional designs would be to adopt Peter Drahos's idea of creating a counter-network to balance that maintained by big pharma. This would


comprise an independent cross-border group of experts that could include Nobel laureates to target a key area of patenting each year. The committee would call that set of patents to account internationally, through submissions to parliamentary enquiries and the media, on the question of whether those patents were increasing or reducing innovation. It would critique patent office administrations for their failures to raise the inventive step in ways that could have better served public health.

One reason why we favour the Drahos proposal is that the deepest problems resulting from the capture of the policy agenda by big pharma are not those of corruption, bad as such problems are. The biggest problem is the same as that which in the second half of the twentieth century struck the second most profitable sector of the world economy, the Wall Street (and London) banking industry. The masters of the universe of Wall Street and of big pharma had over the years been so successful in delivering stupendous profits to their investors that until both fell from grace in recent years their power could as a rule be maintained without corruption. Their power was hegemonic. Hegemony means that those who are exploited come to believe that their exploitation is in their own interests. The exploitation is therefore seen as legitimate. Ordinary people in the United Kingdom looked around their economy in the 1990s and saw industrial wastelands where their country had once led the old industrial capitalism. They could not understand why they were becoming so rich when their economy no longer produced much in the way of goods. The answer that financial journalists provided in response to their puzzlement was that their affluence was mainly created in the City of London (where nothing was manufactured) by bankers who were making the investments that caused their pension funds to grow and grow again. Second, there were high technology IP-based industries like pharmaceuticals that were creating wealth not on the basis of manufacturing pills, but through research. So long as this appeared to be true, the people of countries like the UK swallowed the hook with the bait. Yes, pharma and finance were booming. In fact, however, the business models that underlay their growth were not sustainable.

Finance capitalism had a pathological bonus culture that concentrated profits in the hands of traders, and losses in the hands of pension fund investors. It eschewed risk management in favour of a risk-shifting culture. It sliced and diced risks with derivatives. Derivatives spread those risks around to institutions where little people had their money. Derivatives were also used to hide the unsustainable national debts of countries such as Greece. The United States was too big to fail and felt no need to hide its unsustainable debt. It mortgaged neoliberal capitalism to China’s authoritarian capitalism, which owns a massive amount of US
debt. Banks also befuddled financial journalists with quantitative risk models based on foolish assumptions.

In a similar feat of hegemonic business politics, the western public and journalists have been persuaded by big pharma of the benefits of longer and longer patent monopolies. Policy makers and the public have been left unaware of the historical experience showing what happens to the innovative ability of firms after they have for decades been fattened on cosy monopoly profits. In both cases, hegemony worked because financial risk models and intellectual property law are complex structures. Investors and politicians comforted themselves with the belief that they did not need to understand these things; all they needed to know was that these business models were designed by people cleverer and better informed than themselves. So they should back them. As individuals, all we needed to know was that we could get richer by investing in the firms led by these brilliant figures. In both arenas, the economics profession failed in its function of informing the public debate. There were noble exceptions, but there were also ignoble cases, even involving certain Nobel laureates and other distinguished economists whose scholarship was corrupted by wads of money from fat finance to legitimize its risk models, and big money from big pharma to justify its patent monopolies. By and large the economics profession proved a handmaiden of hegemony, as even Alan Greenspan, the former Federal Reserve Chairman, has now confessed.8 In both cases, it was a hegemony that hastened the foreseeable crisis to which independent but largely unheeded critics had been pointing for decades.

Universities are among the institutions that have been increasingly regulated by states during the era of regulatory capitalism. We saw in Chapter 8 that universities are also the engine rooms for innovation in the biological sciences. We are still passing through a golden era of such innovation. Developing country governments, private foundations and western donors would serve developing nations well by investing in the best biological sciences departments of their universities, particularly with research grant support for innovation in tackling the challenges of tropical diseases. It would be a splendid project for each of the great universities of the world to enter into long-term twinning relationships

8 "I made a mistake in presuming that the self-interests of organizations, specifically banks and others, were such that they were best capable of protecting their own shareholders and their equity in the firms." Alan Greenspan, quoted in (2008), 'I was wrong about the economy. Sort of', Guardian, 24 October. More endearingly, he also said, "I guess I should warn you, if I turn out to be particularly clear, you've probably misunderstood what I've said".
with the developing world so as to ensure that at least one university in each developing nation would become a great research and teaching institution focused on the needs of its own people.

One of the ways in which developing country governments might fund R&D in medicine within their universities is by a tax on the marketing expenditure of pharmaceutical companies, an option discussed in Chapter 8. We saw in Chapter 8 that such a tax would also encourage pharmaceutical companies to grow by investment in R&D rather than in marketing.

When governments and donors fund R&D in universities, policy decisions should not require a choice to be made between keeping the benefits of patents in the public domain and the entrepreneurial trading of patents in the private sector. As we argued in Chapters 8 and 10, there is great scope for hybridity in alternative business models for intellectual property rights, such as open-source biotechnology. A good policy in a new world where there is a sharp increase in the public funding of biotechnology research at universities could be for a marketing arm of the state to advertise globally opportunities for competitive business model bids to exploit important new technologies being developed as a result of such funding. Joint committees of pharmaceutical regulators and researchers from multiple universities could then select the business model bid that would maximize the public health return on the taxpayers' and the university's investment.

11.3 PYRAMID POWER AND A FAINT SPECTRE OF SOCIALISM

Figure 8.2 provides a pyramid of regulatory strategies for drug marketing with a socialist-style spectre at its peak. That particular spectre involves banning all drug marketing and putting responsibility for steering that sensitive task in the hands of a public authority. Of course such a public authority might delegate some of its work to the professions and even to private marketing organizations which would disseminate publicly approved messages on where particular products were and were not likely to be effective and safe – some messages to doctors, others to pharmacists, yet others to consumers. But the pyramid of strategies in Figure 8.2 essentially puts self-regulation in the foreground. Only if that fails will one turn to state regulation. If that in turn fails, then one can turn to punitive taxation. Only if that too fails will one have recourse to a public takeover of the entire enterprise.
Equity fines are another spectre within a capitalist system with some socialist features (Chapter 8). Such fines have potential niche value as sanctions because of the reality of what John C Coffee calls the deterrence trap\(^9\) – the cash fine that is sufficiently high to make it rational to comply might harm innocent employees and damage the local economy. For such reasons a fine sufficient to deter malpractice or to compensate victims is better imposed not as a cash penalty but in the form of a new share issue to finance a victim compensation fund. This dilutes but does not deplete the operating capital of the firm as a going concern.

The script of the film *Wall Street: Money Never Sleeps* is replete with tales of crimes that could not be discouraged without imposing fines so large that bankruptcy and a wider collapse would be at risk. In that sense the storyline is realistic, as is the limited deterrent capability of fear of imprisonment, even for Gordon Gekko, fictional hero of the film, who has already spent time behind bars. Gekko sees himself as having been unlucky to have been sent to jail even though he was not doing anything very different from those around him. Gekko was a victim of another Wall Street banker with a vindictive streak, who informed on him to the Federal authorities. This banker was an even more predatory villain than Gekko himself.

In the real world of corporate crime in the pharmaceutical industry, we have found that during the past half-century of virtuoso corporate criminality, vice-presidents and those of even higher rank virtually never go to jail. China's authoritarian capitalism is a limited but important exception, where one saw that even the head of its Food and Drug Administration was condemned and executed in 2007. The occasional instances of imprisonment that are on record hardly encourage the view that it is the worst of the worst who find themselves behind bars. Even when the head of the Italian drug regulatory authority recently went to prison, the Health Minister above him evaded his considerable involvement in the corruption. One might contemplate once more the well-documented story of Roche executive Stanley Adams who was imprisoned by the Swiss government for “espionage” because he was a whistleblower to European Commission regulators over price fixing for which Roche was subsequently convicted.\(^10\) It is hard to look over the past 50 years of cases across the world in which individuals have


occasionally been severely punished and feel satisfied that at least a very little justice has been done in a limited number of cases. It is even possible to view those convicted through a Gordon Gekko lens – concluding that some may merely have been flawed individuals who became the victims of bigger fish even more venal than themselves. Such individuals are no more than fall guys for the defects of a polluted system. Judges and juries will sometimes be persuaded by talented defence lawyers to view them in this light. This is probably one reason why so few corporate criminals serve long prison sentences.

That said, we would like to see more cases leading to well-justified prison sentences being brought against the corporate criminals of the pharmaceutical industry. We were impressed by the aggressive prosecutorial strategy of then New York prosecutor Rudolf Giuliani that led to the imprisonment of Michael Milkin, the brilliant, flawed financier on whom the Gordon Gekko character is loosely based (with some elements of the real-life inside trader Ivan Boesky mixed in). Giuliani’s strategy essentially involved scanning the horizon relentlessly for insiders who might be nailed and jailed even for relatively minor securities violations. They were told that they were in deep trouble; the only way they could avoid prison was by informing on a bigger fish who had committed a bigger crime. The latter was duly identified and in turn offered the same choice; in this way the prosecutors moved up the chain of authority until they arrived at a really big fish like Milkin. Awarding a string of immunities up a food chain from minnows to sharks is not the fairest way for prosecutors to do their job, though in the Milkin case it served its purpose. All the same, there is a corporate crime enforcement task that remains undone. In the case of the pharmaceutical industry, the failure to do it is costing uncounted lives.

Appreciating though as we do the success of the Giuliani approach of the 1980s, we must also see the shadow side of it. Giuliani’s approach can allow some to conceive of the problem as one that can be solved merely by locking up a few individuals who have misbehaved. That is a dangerous point of view: an insufficiently broad and effective approach by regulators in one case can result sooner or later in the community being exposed to a replay of the same risks in other cases. This was a problem with President Bush’s reaction to the collapse of Enron in 2001; the Bush administration felt that all it had to do was to imprison a couple of tainted individuals and the integrity of American capitalism would thereby be salvaged. The Enron case should in fact have led to serious questioning of the integrity of Wall Street as a system. In retrospect we should feel sympathy with the tens of thousands of innocent employees who lost their jobs in 2001 not only at Enron and Worldcom, but also at
the accounting firm Arthur Andersen, which itself collapsed after criminal charges were laid over its flawed and compromised auditing of these firms.

There is no justice in ruining the lives of these employees. Many regulators, not only those involved with securities, knew that Arthur Andersen was helping various unethical corporations in the 1990s to commit corporate crime.\(^{11}\) If any one of those regulators had called the Arthur Andersen partners together in the 1990s and demanded the kind of sweeping, global assessment of integrity and compliance systems in the worldwide operations of the firm which John J McCloy achieved in the case of Gulf Oil’s international bribery in the 1970s,\(^{12}\) some of the ridiculous bubbles that Arthur Andersen allowed to burst in the United States, Australia and beyond might have been prevented. Instead, when tax regulators in Australia found that Arthur Andersen had allowed a major tax fraud to occur, they settled for a large penalty payout by the offender and an undertaking from Arthur Andersen that they would get rid of the Australian partner who was responsible for the audit.

Brent Fisse and John Braithwaite much earlier made the same point about the large impact resulting from the collapse of the Abu Dhabi bank, BCCI, inflicted on the United Kingdom and beyond in the 1980s (see Chapter 10). If only a single law enforcer in one of the many countries that were concerned about the crimes of BCCI, for example a criminal prosecutor in Florida,\(^{13}\) had demanded a corporate restorative justice process, with the Sheik of Abu Dhabi sitting in the circle with victims, it might have led to a McCloy-style corporate probation report. In that way the wider financial disaster (and indeed the systemic risk to which BCCI for a frightening moment threatened to expose the then fragile British economy) could have been averted. Likewise, as we argue later in this chapter, if Australian regulators had internationalized the Timor Sea oil platform disaster that spewed oil into the sea for 74 days in 2009 as a result of faulty cementing of the base of the drilling apparatus by the US Halliburton Corporation, then that same fault at the hands of the same company might have been prevented from devastating the Gulf of Mexico in 2010.

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In this light, let us return to the somewhat flawed virtue of the Rudolf Giuliani strategy of nailing little Wall Street criminals, threatening them with ruin and prison, and then granting them immunity in return for ratting on bigger rats. That virtue would in our view have been even less flawed had it led up to systemic reform of a major Wall Street finance house, or better, a string of finance houses implicated in systemic abuses. One option is the approach that we see in nursing home regulation in many countries which involves reaching a settlement with the board of directors to fire the top management team and install a group of temporary reform managers approved by the state regulator, with a brief to fix the systemic compliance problems. Another option, provided for under various US laws, is for the regulator to seek a court order under its statute to put the firm into state receivership so that the state can sell it to a more responsible operator as a going concern. The reason that a capitalist state like the US occasionally allows such socialist remedies in the arena of nursing home regulation is that in delinquent facilities the survival of frail and aged patients is at risk.

The public health is however exposed to much greater risks as a result of corporate crime in the pharmaceutical industry. In this light, we believe that the prosecutorial strategy that takes us up from minnows to progressively larger sharks should be available to secure temporary state takeover of a pharmaceutical giant or a Wall Street bank. What we are actually advocating here is transient state control that can catalyse systemic reform and the ethical reinvigoration of a capitalist enterprise. We do not believe that in the long run states are good at managing most kinds of business. However we do firmly believe that in the short term state control can be adopted as a reformative remedy to capitalist excesses. It could be more responsible than a high-profile criminal prosecution that results in the collapse of a firm and loss of the jobs of innocent employees.

Before the financial crisis hit the world in 2008, readers would no doubt have reacted negatively to a “socialist spectre” argument, regarding it as wildly irresponsible. Yet the Obama administration has pushed new laws through Congress that will allow it to more effectively, if temporarily, take over finance houses during any future financial crisis. It managed such state-managed bailouts of banks with considerable difficulty in 2009. During that same year, the Obama administration also socialized and sought to reform systemically the American auto industry.

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(Ford being an exception during this crisis, though it had had its losses socialized in prior crises). For President Obama, that was a bold and high-risk undertaking. It paid off. The auto industry was saved for at least one more decade and the state of Michigan was saved from total economic collapse. Reforms seeking to create a greener American car industry, which would have a better chance of competing with the more environmentally responsible manufacturers of Japan and Europe, have yet to be vindicated, though General Motors' sustainability report for 2013 shows some progress towards cleaner factories and cars. More ambitious hopes for a Green New Deal that could recognize the global financial crisis and the global warming crisis as problems that should similarly be tackled by systemic reform of capitalism have for the present faded.

Nevertheless, critics should take stock of what a watershed it was for a US President in effect to fire the CEO of General Motors and demand a leaner and greener top management team. It was a moment that saved the once greatest commanding height of global capitalism. If it was ever true that “What’s good for General Motors is good for America”, the reality has long been that what’s good for America is a greening of General Motors. Hopefully this greening is what a temporary state intervention has begun to deliver. Or perhaps we will find that the intervention did not bite deeply enough at the peak moment of crisis to deliver a sufficient greening effect.

Our main conclusion at this point must be that imprisonment of pharmaceutical executives is most useful when it serves to demonstrate that it is the grim alternative to cooperating with systemic reform. To put it another way: occasionally sending an executive to jail can be helpful if it conveys the message that this is a just outcome for those executives who refuse to cooperate with enforceable, court-ratified undertakings to transform the rogue culture of their firm into a law-abiding one.

Part of the reform package required here is the transformation of criminal law jurisprudence that Brent Fisse has so long advocated. This reflects a new theory of criminal culpability that regards the highest form of culpability as failure in the aftermath of proven criminal acts to repair harm and tackle the reforms needed to prevent recurrence. The key change is to reconceptualize culpability so that it is no longer proportional to the degree of causal fault. Culpability should in fact be greatest when "reactive fault" is greatest, i.e. when a corporation fails to redeem itself and its industry, when it fails to repair the harm it has done in the wake of proven criminality, and when it fails to sanction the individual executives who are responsible. One might well term this "responsive fault" – a failure to respond to proven criminality at the commanding heights with a credible plan to reform a criminal firm, defining a better path for capitalism to follow and implementing the necessary change in a manner that is both credible and transparent. The Fisse idea is that when a firm fails to respond adequately, a McCloy-style report should be drawn up at the insistence of prosecutors. Such a firm would then be required to hold accountable all individuals within the company who have some individual responsibility for the wrongdoing, and sanction them accordingly. The company would also be required to agree with the court on appropriate corporate sanctions, a firm plan for corporate reform and a compensation package for the victims of their wrongdoing.

Whether or not one shudders at the term "socialism" we believe that we have good reason for contending that temporary state takeovers of wayward firms, in small doses, can help to reinvigorate capitalism and ensure its more sustainable integrity. Invocation of the spectre of temporary socialism by political leaders can provide therapy for a sick industry, and in some contexts at least it will be more creative and less harmful than precipitating the bankruptcy of a major firm, which can only destroy livelihoods and communities. Wall Street bankers and big pharma are not the only industries that could benefit from a spectre of temporary socialism because of the vital national interests they affect. Given the dismal contribution of the ratings agencies, such as Moody's and Standard & Poor's, to the current malaise of that economy, they should surely themselves be subject to a similar analysis. So should military contracting organizations, which contributed through their corruption, fraud and violence to the flawed international intervention in Iraq, or

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those firms that contributed to devastating wars over “blood diamonds” and other resources in Africa.  

The same approach could also be adopted towards the offshore oil industry, in the wake of successive disasters that could progressively devastate the environment, blow out a strained national budget deficit, destroy coastal livelihoods, destabilize the inland economy through pushing up the price of oil, and cause many deaths and injuries to boot, as we saw in the Gulf of Mexico in 2010. Later in this chapter we shall consider the Halliburton Corporation as a further candidate for the spectre of temporary socialism because of the way it has imperilled vital national interests through its work in the Gulf of Mexico, in Iraq and elsewhere.

11.4 A MORE ETHICAL CAPITALISM

A new capitalism could benefit from a new philanthropy. Here there is genuine hope of a more civilized capitalism today. The non-profit Access

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to Medicine Foundation, based in the Netherlands, publishes a biennial ranking of the 20 largest pharmaceutical companies in its Access to Medicines Index. In 2012 GlaxoSmithKline and Johnson & Johnson won the top two rankings. In addition to providing access to medicines in developing countries through philanthropic initiatives, companies are scored on their willingness to discount prices in poor countries, their involvement in research on the neglected diseases of poor people, their transparency and their conduct of clinical trials, as well as their approach to other matters that contribute to access to medicines. While one might question some of the rankings in view of the questionable behaviour of certain firms in matters not assessed in the Index, the Foundation’s approach provides evidence of creative new pressure for a more ethical capitalism from civil society.

Bill Gates stepped away from his leading position in information technology to lead the building of more ethical access to pharmaceuticals in developing countries. What is impressive about Bill and Melinda Gates’s contribution to a new philanthropy is that they have not only given away more than half their own wealth, mainly to relieve the health challenges facing the world’s poorest people; they have also persuaded a large number of other extremely rich people to donate half their wealth to fighting global poverty.

Certain things can more readily be funded by large philanthropic institutions than by states. One such field is that of transformative projects to help developing countries in experimenting with regulatory models for issues such as intellectual property that go to the heart of the interests of big pharma. The foundations have not yet been bold enough to fund this. Elected policy makers have a natural fear of so antagonizing big business that they will be targeted by money politics; offended industry leaders may fund their adversaries or finance media campaigns to smear them and drive them from office. Foundations need not suffer this fear; they are therefore today at least a source of greater hope for investments that can transform patent offices and the process of pharmaceutical innovation in developing countries.

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The resources needed to create a more ethical form of capitalism are to be found not only in foundations funded by capitalists but also within the very corporations responsible for the most criminal conduct. One of the empirical conclusions of this book is that even in the offices and laboratories of the most criminal of corporate actors many ethically minded individuals are to be found, often struggling within the corporation in the hope of making it a force for promoting rather than damaging human health. Astute regulatory policy therefore seeks to link up with these ethically motivated insiders, to understand who they are and to strengthen their arm. While observing government safety inspections of private workplaces, we have often seen a corporate safety officer point the government’s inspection team to a risk that he or she has unsuccessfully sought to eliminate, in the hope that a demand from the government official will result in action. Inspectors who stigmatize entire corporations as irresponsible, who simply seek to maximize corporate sanctions for wrongdoing, fail to identify or recruit such socially responsible allies who can help them to achieve positive outcomes for public health.

We should not be too cynical about corporate social responsibility merely on the grounds that irresponsibility is rife. We are not, after all, cynical about education even though ignorance is common. Corporate social responsibility is a learning project. The idea of the strengths-based pyramid is that networks of concerned reformers can identify where ethical strengths are to be found, even in the worst of organizations, and can both support these strengths and expand them. Our argument is that expanding strengths does more to counter misconduct than does targeting weaknesses. An ethical culture that is nurtured to grow from its own roots will be more resilient than one forcefully transplanted from outside. More than that, ethical capitalism can become more dynamically variegated and innovative if it is encouraged to grow in the soils of disparate corporate cultures. One of the problems with Corporate Integrity Agreements (see Chapter 10), such as have become more widespread in the United States, is that they foster an ethical monoculture; in effect they provide a template of boxes that must be ticked. Corporate Integrity Agreements will never promote managerial innovation in compliance and integrity systems if they are expected to follow standardized requirements.

Here again it is instructive to examine the regulation of US nursing homes. Twenty years ago a regulation was introduced that required each home, after consulting with its residents’ council, to convene a meeting of its staff and management to select a particular problem in the quality of care that called for a solution, and to secure improvement within the ensuing year. This involved designing a plan to improve the situation,
implementing that plan and then determining in due course whether the plan was proving successful. The law does not tell the facility which is the right problem to select or what the right way is to solve it. It finds no failure to comply if the evaluation shows that a promising plan has not worked. It is a law that simply requires organizations to think and act on what they believe is the best way to ensure continuous improvement. Even more innovative Australian laws now similarly encourage this kind of creative selection of continuous improvement objectives. These laws strike us as providing a sound approach for nurturing diverse forms of innovation to improve ethical cultures in any sector.

11.5 A NEW DRUG DIPLOMACY: A BRIC CAPITALISM OF OPEN-SOURCE START-UPS?

The rise of Brazil, India and China in international affairs could or should offer hope of a new drug diplomacy. South Africa has often coordinated African engagement with these countries in trade diplomacy. The fourth member of BRIC, Russia, while not yet having shown leadership on drug diplomacy, has interests similar to those of Brazil, India and China in this area. These countries are the fastest-growing part of the world economy; they account for more than a third of the planet’s population and have formidable clout in the world system. They possess rapidly growing middle-class markets for pharmaceuticals. They are also now demonstrating leadership in developing industrial capability and exhibit promising growth in R&D competence.

BRIC universities continue to advance, although in the biological sciences they do not yet approach the standards of the great research universities of North America and Europe. This is their weakness in mounting a challenge to the hegemony of protracted western patent monopolies through compulsory licensing, new paradigms of patent office administration and hybrid business models. At the same time, this weakness means that it does not make sense for BRIC to succumb in the pharmaceutical sector to the same pattern of dominant capitalism that exists in the West, as has happened with respect to the manufacture of white goods and countless other products. The only way in which these

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22 These laws have been far from perfectly implemented in both the US and Australia, but even so they are a platform on which a transformation of the aged care industry might be built. For a detailed discussion of these reforms see Braithwaite et al., *Regulating Aged Care*, op. cit.
countries can effectively stand up for the interests of their medicine consumers and develop their own distinctive productive capabilities is to forge hybrid business models. These will need to marry their productive/marketing capabilities to the R&D that can be networked into China, India, Russia and Brazil from the world's great universities. As compared with the big pharma of the West, industry in the BRIC countries has a far greater interest on behalf of both their customers and their latent drug marketing/production capabilities in seeing new open-source biotechnology start-ups flourish.

These states should therefore be willing to compete with big pharma in paying to acquire open-source biotechnology start-ups, and they should be ready to show more respect for the open-source philosophies of their founders. Obversely, open-source idealists in and around the fringes of western universities and research institutes need to recognize this opportunity more clearly. They must understand that when they are courted by big pharma, the interest of the latter lies frequently in neutralizing them. Western start-ups might do better to turn to Brazil, India, Russia, China and South Africa to persuade them to develop an industrial policy that circumvents western intellectual property hegemony. That is happening only to a very limited extent, though there is an emergent symbiosis of interest. Brazil, India, Russia, China and South Africa have a greater interest in developing western open-source businesses than does western big pharma. Open-source start-ups have an interest in developing links to these five countries through non-hegemonic, non-western business models.

11.6 FORESEEING THE UNFORESEEABLE IN DRUG DIPLOMACY

It is of course impossible to foresee where drug innovation would head were it grounded in new BRIC industrial policies involving hybrid approaches to intellectual property rather than in continuing support for patent monopolies valid for 20 years or more. Innovation could then be grounded in a new openness of western biotech start-ups, propositioning the custodians of BRIC innovation policy to engage in partnerships with their pharmaceutical industries. It is impossible to foresee where such repeated partnering would head; it could move in various directions. Indeed, if we could foresee its future course it would hardly constitute a genuine model for business innovation. All the same there is a degree of virtue in the ability of reformers to predict just a little of the unforeseeable, so long as they understand that dynamism will yield transformative
moments of an unpredictable nature. If networked governance of the industry were to succeed in unleashing a new era of dynamism, ethics and innovation, new technologies could lead the industry to places that none of us can imagine. The globalization of disease is just one such uncertain dynamic. This "certainty of uncertainty" reinforces the wisdom of our core message in Chapter 8 that a new regulatory capitalism for drug markets will need to be responsive and networked, covering the weakness of one approach with the strengths of another. And it must be iteratively open to subsidiary tracks of drug diplomacy, bringing with them new visions of how to peer a little further into the unknown. In this book we have argued that such NGOs as Healthy Skepticism, Oxfam, Médecins sans Frontières, Taxpayers Against Fraud and Health Action International are important as stimulants for and participants in the kind of networked governance of the pharmaceutical industry that is required. We return to the idea of second-track drug diplomacy later in this concluding discussion.

Perhaps the biggest obstacle to a new drug diplomacy in the BRIC countries is that the industry policy thinkers of BRIC still lack the imagination to see any path ahead other than that of outperforming the West, using purely western business models but benefiting from their cheaper domestic labour pool and privileged access to their own burgeoning domestic markets. Peter Drahos finds indications that this is the way that the BRIC countries are heading at the moment, captured by elites who have an interest in patents, who are unresponsive to the public interest in securing access to affordable medicines and who turn their backs on BRIC's potential ability to lead the G-77 group of developing countries in matters of drug diplomacy. If this continues, they will pay a heavy price for their want of imagination. China and India can outperform western capitalism in the production of white goods and cars given their vast domestic markets, industrial discipline and cheap labour. That formula will not however allow them to outperform the innovative sectors of western capitalism. University-based western start-ups may also lack the imagination to develop their business models in harness with a progressive BRIC drug diplomacy. That may well create a risk for them since, in the course of the present century, Asian universities could well overtake them through being bold enough to seize those new opportunities. One must hope that leadership will emerge in Asian,

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Brazilian or African universities that is responsive to the needs of the people of these countries for bold and strategic drug diplomacy.

On the positive side, western business model hegemony is a more fragile thing than it seems. It no longer delivers the super-profits of the later decades of the twentieth century. While certain dominant western economies – the United States, the United Kingdom, Germany, Switzerland and a very few others – have a profound economic interest in propping up and extending the long patent monopoly model, most western economies do not. Canada, Australia, New Zealand and most European economies are net importers of intellectual property rights in drugs. It is not only the poor countries of Africa and Latin America that have an interest in supporting a BRIC bold enough to transcend the long patent monopolies that make their drug imports so unaffordable. The newly industrializing economies of ASEAN, such as Indonesia, and the Asian Tigers – Korea, Taiwan and Singapore – are likewise net importers of intellectual property rights in drugs; indeed massively so. The drug diplomacy interests of Japan in supporting its ageing population, who are huge pharmaceutical consumers, are less clear. It is uncertain whether Japan is or is not, or could become, a net exporter of intellectual property rights in drugs.

Even in the country which is by far the heftiest net exporter of intellectual property rights, the United States, the hegemony of big pharma is in fact fragile. The United States is also the home of most of the biotechnology firms that mushroom on the fringes of its great universities and that could grow faster by opting for alternatives to partnering with big pharma. The US consumer movement is vibrant and is educating its citizens to the fact that on average they die younger than the people of many poorer countries. Meanwhile the Canadian challenge is becoming formidable, with many Americans now travelling across the border to Canada to purchase more affordable life-saving drugs.

It is not only the poorest Americans who cannot afford medicines. Advocates on behalf of US consumers, such as Public Citizen, are a constituency for a new drug diplomacy. The richest American, Bill Gates, became, as we have seen, the leader of a new philanthropy that can be a crucial element in a new deal for the world’s drug consumers. What a paradox that a man whose wealth was created by intellectual property rights – admittedly copyright rather than patents – has become a strategic contributor to the emergent hybridity and fluidity of drug diplomacy. His foundation is open to supporting research by start-ups with the potential to conquer tropical diseases. Critics call the Gates Foundation “philanthrocapitalism” or “venture philanthropy”. They say it funds through personal networks rather than through transparent processes of
independent review. Doubtless it could be more transparent. \textsuperscript{24} Perhaps, however, we should welcome competition to the old philanthropy from a new philanthropy that is better connected to capitalist networks, that is open to start-up networks, that offers both unprecedented amounts of new money and new hybridity and that can move faster than traditional philanthropy, even if it is not so accountable.

11.7 PHARMA’S ETHICAL DISSENTERS

One of the arguments of this book has been that within US pharmaceutical companies there are countless people with consciences as genuine as those of Bill and Melinda Gates. The senior author of this book became a reformer as an ethical dissenter employed by the industry. Many other insiders have over the years sought – and often found – opportunities to move away from industry and to work for regulators, for universities, for the WHO or for NGOs that support access to drugs in developing countries. Many today are on the lookout for opportunities to work for drug innovators with business models that enlarge the intellectual commons. Ethical dissenters within big pharma can be key players in crafting hybrid business models that circumvent the dead hand of the monopolies for which many of them acquired disdain after experiencing them on the inside. These are the professionals who whisper in the ear of an inspector where to look to find an unsafe manufacturing practice (Chapter 2), who secretly report to the FDA on cover-ups of the side effects revealed in clinical trials of a new drug (Chapters 1 and 5), who on occasion blow the whistle and can make \textit{qui tam} work as a transformative enforcement innovation (Chapter 10).

Any capitalist hegemony is by definition an architecture resting on strong pillars. In this case, the pillars are acceptance of the hegemony by industry analysts serving the stock markets, acceptance by ratings agencies, and the capture of political leaders, patent offices, bodies like the World Intellectual Property Organization and the World Trade Organization, the TRIPS agreement and countless bilateral trade agreements that guarantee and expand monopoly rights; there is also the pillar of intellectual property law as a mostly servile institution. We have however seen that these pillars show many cracks, that the architecture is vulnerable to historical crisis, to moments when corporate crime is exposed, and to moments when temporary “socialism” might well be

used to transform firms that fail the public health. Just as not all intellectual property lawyers are servile to a global intellectual property order that denies most people of the world the right to safe medicines, we have seen that not all employees of big pharma are without hopes for transformation of that order. The US Patent and Trademarks Office (partly under pressure from the courts) has at times instituted reforms to render its conferrals of monopoly privilege more susceptible to challenge by outside critics. An example is what has been termed the “marriage of Wikipedia to the authority of Administrative Law” through an open review process.\(^\text{25}\)

The hegemonic order is thus now subject to threats from within and threats from below – from start-ups with alternative business models, from development NGOs such as Oxfam that urge developing countries to contemplate a new trade diplomacy. Then there are threats from above – hopefully in the future from growing numbers of political leaders like Republican Senator Howard Grassley who introduced the False Claims Act in 1986 and has successfully pleaded for some expansion of its scope since that time.

One might have hoped that the World Health Organization would be an important vehicle, or at least a site, for a new drug diplomacy. WHO diplomacy has been a disappointment to reformers. At times it has been manipulated astutely by big pharma (Chapter 4). The 1988 debates over the WHO Ethical Criteria for Medicinal Drug Promotion could be characterized as involving competition among the most powerful states to secure maximum freedom of action for their pharmaceutical champions rather than being an effort in good faith to strengthen global public health capacities. We do not wish to belittle the significance of the notable contributions that the WHO has made, for example by promoting and applying the concept of the “essential drugs” that should be available in all developing countries, but much appears to depend on a few brave individual leaders. It is notable that the adoption of Essential Drugs Policies in the mid-1980s in the face of virulent opposition and ridicule from the western pharmaceutical industry was substantially due to the role played by two individuals with a clear understanding of the issues, namely Halfdan Mahler as director general and Ernst Lauridsen as head of WHO’s Essential Drugs Programme. Observers of the Geneva scene are all too familiar with the role played by the International Federation of Pharmaceutical Manufacturers Associations at meetings of the World

Health Assembly. By contrast, much appears to have been quietly achieved by WHO’s six Regional Offices which maintain close links with national authorities and have often been instrumental in assisting weaker member states to formulate and implement national pharmaceutical policies.

11.8 SECOND-TRACK DRUG DIPLOMACY

While “first-track diplomacy” in the halls of the World Health Organization has led to many disappointments, there are incipient second tracks of diplomacy that engage more socially responsible elements in the industry with reformers like Bill Gates, reform-minded national drug regulators, Indian open-source portals and second-tier officials of the World Bank and the network of critics underpinning organizations like Oxfam and Health Action International. These second tracks have been part of what has allowed the Gates Foundation’s highly politicized and publicly debated “venture philanthropy” to achieve what it has. Another second track of importance to the analysis in this book is the epistemic community of pharmaceutical regulatory compliance professionals that meets as the Regulatory Affairs Professionals Society.

Nothing that has happened so far in these networks of concerned advocates, experts and second-tier stakeholders has fundamentally shaken the pillars of big pharma hegemony. This book can be read as a contribution to those second-track conversations, providing some suggestions as to how to think about the nature of the medicines crisis and what to advocate in the networks of second-track drug diplomacy. The hope is that if players as powerful as Bill Gates, assorted former health ministers and Nobel laureates do participate in those second-track conversations, some reforms will gather momentum at moments of crisis, or in situations of proven criminality, which are the special focus of this book.

Peter Drahos’s idea of a counter-network that would call sets of patents to account before parliamentary committees and other forums around the world is another second-track idea. We would submit that a vision for networked governance and transformation of the industry, emerging from various such networks, can inspire people both within and outside the industry. One of the ways in which reformers must foresee the unforeseeable is to be prepared with transformative agendas that can be implemented when future crises shake confidence in the hegemonic order. Such crises may for example result from an inadequate response to some catastrophic incident of bio-terrorism, or from society’s failure to face up to some future pandemic that results in a much more extensive
and better founded global panic than did the 2009 swine flu alarm. While we cannot know which crisis might usher in change, we can be sure that, when the pillars of the hegemonic order are so cracked as is now the case, when the industry remains so unresponsive to the public interest and so distracted from genuine innovation, and when profits are falling, there is an unprecedented opportunity to fight for strategic transformation.

One of the things that makes big pharma vulnerable is a corporate culture attuned to society’s tolerance of corporate law breaking. That tolerance could crumble. We considered in Chapter 10 the new potential offered by privatized enforcement when public law enforcement is hampered by the dominance of major pharmaceutical companies that are more powerful and better resourced than many governments. We argued that this potential for privatized enforcement, especially through refining old ideas of *qui tam*, is particularly relevant for developing countries.

In theory, the jurisdiction of the International Criminal Court might ultimately be extended to embrace corporate crime in the pharmaceutical industry. In practice however the largest exporter of pharmaceuticals, the United States, refuses to submit to the jurisdiction of international criminal law. The International Criminal Court is in any case already overwhelmed by its core business concerning crimes against humanity in times of war, and unable to keep up with even the very worst cases of this type brought before it. One of the things that the incipient second-track drug diplomacy referred to above has achieved is much improved bilateral and regional cooperation on enforcement against pharmaceutical companies. The European Union has advanced furthest in bringing about such regional cooperation. Within the Association of Southeast Asian Nations (ASEAN), the Caribbean Drug Collaboration and cooperation within the South African Development Community on such matters as access to medicines, pooled drug procurement and traditional medicines, one also observes the emergence of collaborative arrangements through which formal and informal enforcement can be facilitated.26

11.9 McCLOY AND GIULIANI RENEWED

Reformers cannot but be disappointed by the quality of the Corporate Integrity Agreements that have been negotiated with pharmaceutical companies following False Claims Act suits in the United States. We see

them as having become templated and disconnected from the specificities of the harm caused or the depth of the wrongdoing in which a particular company has indulged. There has also been a want of imagination in enforcement that extends investigations across national borders, in public reporting and in the reform ideas that can be built into Corporate Integrity Agreements. John J McCloy’s 1976 report into the bribery activities of the Gulf Oil Corporation across many nations remains a model for what can be achieved but is rarely attained.  

Bold regulators in any country, even a country where it is not possible to point to the spectre of *qui tam* and to equity fines as the alternative to full cooperation, can still threaten a prosecution that might lead to imprisonment and large fines. Such threats could be sufficient to spark internationally wide-ranging Corporate Integrity Investigations and Agreements. When a company is found to be putting lives at risk in many countries, the correct thing for an ethical regulator at the national level to do is to save the greatest possible number of lives across the world. It can often achieve that by cutting a deal; a waiver of criminal prosecution for the crimes committed in that one country can be offered in return for disclosure of the compliance problems across all the company’s operations in all corners of the world and a solemn undertaking to implement a monitored and publicly transparent plan to reform the corporation and replace criminal executives with responsible individuals. Bold, imaginative and internationally sweeping Corporate Integrity Investigations and Agreements following egregious corporate crimes committed by the pharmaceutical industry might also contribute to the creation of a sufficient climate of political concern to demand radical transformation of an industry that is failing to deliver the right to safe medicines. One would hope to see as strategic players in the new drug diplomacy a new generation of John J McCloys and Rudolf Giulianis who will prove to be cosmopolitan prosecutors with a global imagination.

As we argued earlier in our study, pharmaceuticals is not the only industry that poses truly major risks to public well-being. In seeking solutions to major problems in this sector we need to benefit from experience gained in others as well. The nuclear industry provides one example. Following the 1979 Three Mile Island disaster in Pennsylvania, which very nearly led to the meltdown of a nuclear reactor, the public spotlight was thrown upon a variety of problems within the industry and its mode of regulation. In the wake of the public scrutiny that ensued,

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nuclear safety regulation was transformed, not only in the United States but in every country in the world dealing with nuclear energy, resulting in a reduction of SCRAMS (i.e. automated emergency reactor shutdowns) worldwide to less than one-tenth of their frequency prior to the public disclosures concerning the events on Three Mile Island.\(^{28}\)

In other sectors, national regulatory failures have unfortunately all too often been contained within national politics. To take another concrete case, when Australia in 2009 suffered an offshore oil blowout from a drilling platform in the Timor Sea that could not be capped for 74 days, the diagnosis of the causation of the spill by the defective concrete base of the well that had been installed by Halliburton Corporation\(^{29}\) was not applied internationally.\(^{30}\) As part of its enforcement response, the Australian regulator could have insisted that Halliburton retain engineering consultants to determine whether any of the other offshore wells that it had cemented worldwide posed a similarly catastrophic risk to the world’s oceans. Unhappily, the historical record shows that the Australian regulator did not do so. The following year a British Petroleum drilling base in the Gulf of Mexico, which had been cemented by Halliburton, also failed many months after the Timor Sea disaster, causing a further environmental catastrophe. It took 86 days to cap that well. Particularly in view of the fact that only two companies, one of which is Halliburton, dominate the world’s well cementing business, the Timor Sea tragedy could and should have focused the world’s attention on a 2007 study by three US Minerals Management Service officials, which concluded that


\(^{30}\) The subsequently released Commission of Inquiry concluded: “The source of the Blowout is largely uncontested. While the Inquiry received submissions advancing several theories, it is most likely that hydrocarbons entered the H1 Well through the 9% cemented casing shoe and flowed up the inside of the 9% casing. The Inquiry finds that the primary well control barrier – the 9% cemented casing shoe – failed.” See Borthwick D (2010), ‘Report of the Montara Commission of Inquiry’, Government Montara Commission of Inquiry, Canberra, Australia, p. 7.
“cementing was a factor in 18 of 39 well blowouts in the Gulf of Mexico over a 14-year period”.31

Vioxx®, thalidomide, Three Mile Island, the Timor Sea and Gulf of Mexico oil platform tragedies, and integrity failures of ratings agencies that have contributed to a crash and a recession – these are the sorts of wrongs that should always force society to insist on broad and effective Global Corporate Integrity Investigations and Agreements. And these reactions need to be far-reaching, international, rigorous and publicly debated. Corporate crime scholars in our universities should be showing more leadership in framing such debates. Crises create special opportunities for transformation. Yet these are usually missed. Industries like the global nuclear industry of the 1970s, the global ratings and derivatives markets of the 2000s, the pharmaceutical, offshore oil and private military contracting industries of the 2010s are in a special category. These corporations commonly fail to deliver the profound benefits that we might hope for. Yet at the same time they pose grave risks to interests as vital as public health, energy security, environmental security, financial security and the security of entire nations.

When a massive betrayal of public trust in a particular business sector occurs, we must denounce any national regulatory body that fails to expose internationally the integrity failures of that industry and ensure the necessary transformation. Corporate crime enforcement that is internationally entrepreneurial is one key that could unlock the desperate need for a new international drug diplomacy. It is not the only key, just a neglected one. That is why we have explored it in this book.

31 Gold and Casselman, ‘Drilling process attracts scrutiny in rig explosion’, op. cit.
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