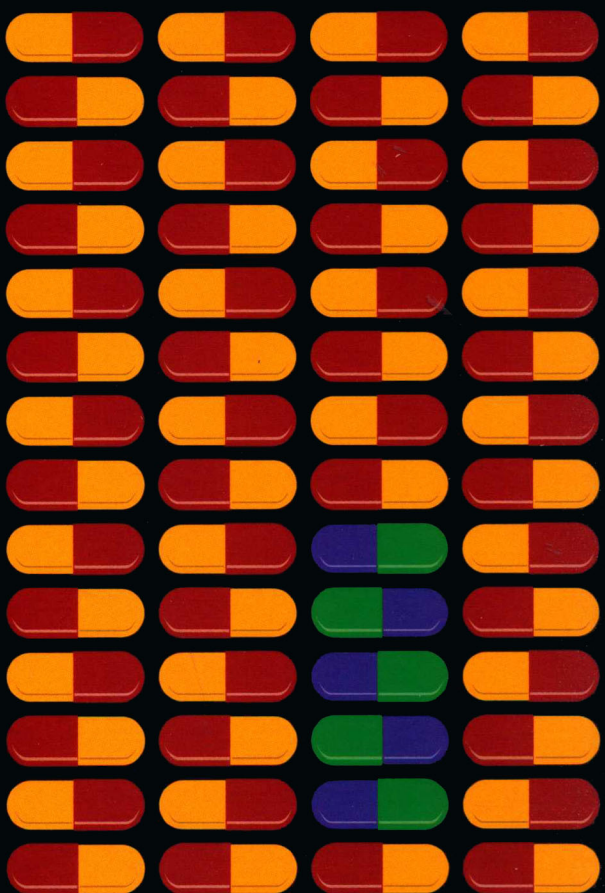
Law and the Regulation of Medicines



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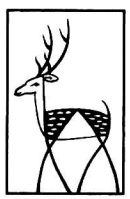

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LAW AND THE REGULATION OF MEDICINES

The principal purpose of this book is to tell the story of a medicine's journey through the regulatory system in the UK, from defining what counts as a medicine, through clinical trials, licensing, pharmacovigilance, marketing and funding. While the UK's regulatory regime is the principal focus, the question of global access to medicines is addressed not only because of its political importance, but also because it is an issue which places the question of whether medicines are a private or a public good in particularly stark focus. Two further specific challenges to the future of medicines regulation are examined separately: first, pharmacogenetics, or the genetic targeting of medicines to subgroups of patients, and second, the possibility of using medicines to enhance wellbeing or performance, rather than treat disease. Throughout, the emphasis is upon the role of regulation in shaping and influencing the operation of the medicines industry, an issue which is of central importance to the promotion of public health and the fair and equitable distribution of healthcare resources.

In memory of my brother, Rupert Jackson
1968–2002

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PREFACE

In some quarters, there continues to be scepticism over medical law's claim to be a distinctive area of legal scholarship, as opposed to a melting pot of tort, criminal, family and public law with some applied ethics thrown in for good measure. What is uncontroversial, on the other hand, is that some medico-legal questions have received much more academic commentary and analysis than others. Lawyers are often drawn to the complex issues that arise in malpractice litigation and in applications for judicial review, and it is easy to see why academics, as well as the general public, are fascinated by the complex and thorny ethical issues that arise at the beginning and end of life. Clashes between and autonomy and other values, such as beneficence or the public good, are played out in debates over the best way to solve the organ shortage. Medicines regulation, in contrast, has attracted comparatively little attention.

I do not mean to suggest that the regulation of medicines has been ignored altogether, although it is noteworthy that, within the UK, sociology journals are more likely than law journals to contain articles devoted to defects or gaps in the regulation of medicines. There are a number of scholarly works which explain the increasingly complex web of European Directives; indeed, given the impact of the EU on medicines regulation, it has clearly represented an important case study in the field of European law. There is also a burgeoning literature, much of it coming from the US, describing alarming, not to say shoddy or even downright illegal practices in the pharmaceutical industry.

At the risk of drastic over-simplification, analysis of medicines regulation tends to fall into one of two camps. Either it explains, describes and evaluates existing regulation, or it draws attention to the negative consequences of drug companies' relentless pursuit of profit. My purpose in this book is to try to steer a course between these two poles by concentrating on the way in which regulation shapes behaviour. It should not surprise anyone that a for-profit company, which is under a duty to maximise shareholder value, will strive to increase its profits within the rules that constrain its activities. Those rules are therefore critical, since both their content and their implementation will largely determine the limits of what the pharmaceutical industry can do, and therefore does, in its pursuit of the bottom line.

To take a concrete example: many commentators are critical of the fact that drug companies often seem to be more interested in developing 'me-too' drugs – that is, new versions of existing profitable medicines – than they are in discovering novel treatments for neglected diseases. In practice, however, castigating drug companies for acting in the best interests of their shareholders diverts attention away from the role that the law plays in *facilitating* and *encouraging*, albeit not

intentionally, the development of drugs that do not offer much, if any, improvement over existing and well-tolerated medicines. Rather than worrying about why drug companies do not behave more like charities, we should instead focus upon the regulatory framework which specifies the essential prerequisites for receiving a licence to market a new medicine. If it is only necessary to prove that a drug is safe and marginally more effective than nothing, then this is what clinical trials will set out to prove. There is no point in lamenting the fact that many new drugs offer no improvement over established medicines if such a requirement is absent from the criteria which must be satisfied before a marketing authorisation can be granted.

The pharmaceutical industry is a global one: a series of mergers towards the end of the twentieth century means that a handful of supranational companies are now responsible for developing and supplying almost all branded medicines worldwide. These companies are extraordinarily powerful, and countries which institute hostile regulatory regimes may find that important sources of employment and tax revenues simply move abroad. It would probably be impossible to institute a uniform global regulatory system, although attempts at harmonisation of certain aspects of the licensing process do exist. Nevertheless, while this book concentrates on the UK, and inevitably also the European legal framework, the way in which the development and supply of medicines is regulated in other parts of the world is also important. Clinical trials, for example, commonly cross national borders, taking place in many countries simultaneously. If a UK-based company is carrying out research in India, the Ukraine and Japan, for a medicine which it intends to market worldwide, whose rules should govern the conduct of those trials?

Although it is important not to ignore the global reach of the pharmaceutical industry, the UK offers an especially interesting site for investigation of what might be described as a clash of cultures between for-profit drug companies and state-run healthcare provision. At the time of writing, there is much greater private involvement in the supply of healthcare in other high-income countries than there is in the UK. In Australia and in most European countries, state funding for healthcare exists in tandem with private insurance, and reimbursement schemes are more common than Aneurin Bevan's vision of the NHS as a comprehensive healthcare system, free at the point of use. Of course, in the US, the healthcare system is thoroughly saturated with for-profit companies that provide health services, manage care and offer insurance schemes.

It seems likely that recent reforms to the NHS will give a greater role to private providers, but nevertheless the UK has a long and proud history of publicly funded and state-run healthcare provision. Obviously, the treatment we receive within the NHS is not limited to medicines, but equally they are an important aspect of the care which the NHS provides, and critically, they are developed and supplied by the private sector. Imagine that an orthopaedic surgeon working in the NHS develops a promising new way to treat torn knee cartilage. The surgeon's first step will not be to obtain a patent for his new technique and prevent anyone else from carrying out surgery in the same way for 20 years. Rather, the surgeon is likely to

seek to publish his results in a medical journal and discuss them with colleagues. In contrast to this public-service ethos, the development of a new medicine is treated as a private good, to be patented and profited from, even though, like the innovative surgeon's salary, it will be paid for by public funds.

The lack of fit between the private and public good models of healthcare provision is an important theme that emerges in several different contexts in this book. One particular point of pressure is the moment at which a medicine's chemical formulation moves from being a trade secret, protected by patent law, to being part of the publicly available 'knowledge commons'. Deciding to grant manufacturers 20 years of patent protection enables them to recoup their costs and make a profit, but it inevitably does so at the expense of making medicines available cheaply more quickly. Of course, in theory the patent system also protects public health by creating an incentive towards innovation. In practice, however, because it is possible to patent medicines which do not represent a 'step-change' for patients, patents incentivise the development of profitable medicines, and these are not always necessarily especially innovative.

The chief purpose of this book is to tell the 'story' of a medicine's journey through the regulatory system in the UK. First, it is necessary to define what a medicine is, and what it is not, and this means contemplating where alternative and complementary medicines might fit within the regulatory scheme. Next, the medicine must successfully complete the various phases of clinical trials in order to gather evidence sufficient for it to be granted a marketing authorisation. Once a medicine is licensed for use, it continues to be monitored, and if safety problems emerge, litigation is possible. After licensing, the medicine's manufacturer will market its new product, to both prescribers and consumers, and decisions must be taken within the NHS about its affordability.

While the UK's regulatory regime is this book's principal focus, it quickly became apparent that a book on medicines regulation which ignored global access to medicines would fail to address an issue of growing political importance, and one where the question of whether medicines should be treated as a private or a public good comes into particularly stark focus. As a result, the chapter on the funding of medicines within the UK is followed by one which addresses global access to medicines and vaccines.

Two further specific challenges exist to the future of medicines regulation, and these are dealt with separately in the final two chapters. First, it is possible that pharmacogenetics might end the blockbuster model of drug development, whereby medicines are developed for the population as a whole. Genetic testing could enable medicines to be targeted much more specifically to subgroups of the population in whom they are likely to be safe and effective, and while this could have obvious health benefits for patients who receive effective treatment more quickly, by shrinking the potential market for new medicines, it also raises a number of distinctive issues. What will happen to people with rare genotypes for whom it will not be profitable to develop medicines? Unlike genetic testing that can identify future susceptibility to disease, pharmacogenetic testing might reveal that

someone will be largely untreatable in the future. Routine pre-prescription genetic testing might also raise new confidentiality issues, and although patients would have the right to refuse testing, this might decrease their access to medicines.

Second, we normally think of medicines as something we take when we are ill, to restore us to health or to alleviate our symptoms. Of course there have always been exceptions to this: the contraceptive pill is a good example of a medicine which is intended to improve quality of life by enabling women to control their fertility. The development of more medicines which are intended to enhance well-being or performance, rather than treat disease, has led to interest in whether we might be entering a new era of cosmetic pharmacology, in which taking medicines may be a lifestyle choice, rather than a public health good. Does enhancement medication raise any special ethical issues – is it cheating, for example, and should it be routinely available within the NHS?

Throughout, I hope to demonstrate that law and regulation are important 'actors' in the development and supply of medicines. This is not to anthropomorphise law, rather it is to argue that those responsible for the content of the regulatory regime, and the way in which it is administered, play a crucial role in shaping the development, supply and marketing of medicines. If we believe that drug companies devote too much energy to developing new treatments for obesity and male-pattern baldness, and not enough to finding cures for sleeping sickness and dengue fever, we should acknowledge that the regulatory framework may help to create or sustain incentives towards the former, and disincentives towards the latter. If we are concerned about the indirect marketing of medicines to consumers, through disease awareness campaigns for example, then attention should be paid to the existence of easily exploitable loopholes in regulations which are supposed to restrict the advertising of medicines.

In sum, we all benefit from the wide availability of safe and effective medicines, which may be facilitated by creating the background conditions in which the pharmaceutical industry can flourish and be productive. At the same time, the pursuit of profit will sometimes be in tension with the promotion of public health. We need to be alive not only to the intended but also to the unintended consequences of regulation, and to the understandable tendency of large multi-national companies to seek out and exploit any potentially profitable loopholes and cracks in the regulatory regime. We should not be surprised that for-profit companies are motivated by the pursuit of profit, rather our focus should be on the role of regulation in shaping and influencing the way the medicines industry works. This is not to say that regulation is the only relevant factor, nor that changing the status quo will always be easy, or even possible. Rather, what I hope this book will demonstrate is that regulating the development and supply of medicines is not only a complex and challenging task, but also one that should be of central importance to anyone interested in the promotion of public health and the fair and equitable distribution of healthcare resources.

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What are Medicines and why are they Special?

OBVIOUSLY, THERE ARE points of similarity between the design and manufacture of pharmaceutical drugs and other products. Computer manufacturers are also under considerable commercial pressure to come up with new and improved computers, and novel technological gadgets. Like drug companies, they must continually innovate in order to remain profitable. The food industry makes products for human ingestion, and, in common with the pharmaceutical industry, its reputation will be badly affected if an unsafe product causes its consumers to become ill.[1] Despite the existence of similarities with other industries, one of the key assumptions underlying this book is that there is something distinctive about medicines which necessitates a special regulatory regime.

This chapter begins by examining, in very general terms, what it is that makes medicines special. Next, it considers how medicines are defined by law, and the difficulties that can sometimes arise in telling the difference between medicines and other products, like vitamin supplements and homeopathic remedies. The line the law attempts to draw between medical and non-medical products depends both upon the claims made for a product's efficacy, and upon the nature of the substance itself. Complementary and alternative medicines are subject to a special regulatory regime, where the burden of proof of efficacy is different from that which applies to conventional medicines. This chapter will conclude by arguing that the reasons which justify treating medicines differently from other products apply whenever someone claims to be able to cure disease or relieve symptoms, and that, as a result, purveyors of alternative medicines should either have to prove effectiveness in the same way as manufacturers of conventional medicines or stop making medical claims for their products.

I Why Medicines are Special

The claim that medicines are unlike other products has two components. First, there are the *intrinsic* properties of medicines, which must be powerful enough to

[1] I Sample, 'E Coli Outbreak: German Organic Farm Officially Identified' *The Guardian* 19 June 2011.

alleviate symptoms or alter disease progression. Any compound which is potent enough to have these positive effects may also be potent enough to cause adverse side effects in some users. Even common and generally safe drugs like aspirin are not safe for everybody: in children, aspirin can cause Reye's disease. And treatments for life-threatening diseases, like cancer, are so toxic that they cause extremely unpleasant side effects in almost everyone. The sort of risk-benefit calculation that makes it acceptable to market a drug which has very serious side effects, even when taken exactly according to instructions, would not make sense in relation to other products for human ingestion. A substance which is inert enough never to cause adverse side effects is also likely to be too inert to cure disease. If every licensed medicine had to be wholly safe for the entire population, there would be few treatment options available. The question then becomes whether a medicine is *safe enough* to license for use in humans, rather than whether it is 100 per cent safe for everyone.

The second and related aspect of the claim that medicines are special relates to how they are purchased and used. Here there are important differences between medicines depending upon how consumers obtain them. Some medicines require a prescription written by a doctor or a nurse prescriber; others can be purchased, but only in a pharmacy staffed by a qualified pharmacist; others are available for general sale, in pharmacies but also in supermarkets and convenience stores. Chapter three considers this subdivision in more detail. For now, the important point is that general sale medicines, like paracetamol and ibuprofen, are not that different from other consumer products. People can purchase and take them without the intervention of a professional intermediary. Limits on packet size and on how many packets may be purchased simultaneously are intended to discourage overdose, but it is clear that these are ineffective obstacles to someone who is determined to obtain large quantities of, say, paracetamol. The local chemist may only be prepared to sell me two packets of sixteen tablets, but I could very easily visit a number of other shops in order to amass sufficient pills to cause serious harm to myself.

Pharmacy medicines are subject to slightly more control. For example, the sale of a commonly used pharmacy-available sleep-aid will be accompanied by a reminder that it is for occasional use only. Where there is a contraindication to the use of a pharmacy-available medicine, the pharmacist will be able to ask the customer whether they have diabetes, say, or high blood pressure. Of course, the pharmacist is not able to insist upon proof that the person buying the medicine is telling the truth, so this level of control, while more intensive than that which exists in relation to general sale medicines, is still imperfect. This means that where medicines are available for sale in pharmacies, they should not be so unsafe that there are likely to be very serious consequences if they are used either by people with contraindications, or more frequently than is advisable.

It is the category of prescription-only drugs which are sold, purchased and consumed in a wholly different way from any other consumer product. When a medicine is prescribed by a doctor, the person who makes the purchasing decision is

not its ultimate consumer. A person may visit their doctor and ask to be prescribed antibiotics or sleeping pills, but they have no right to a prescription. If the doctor believes that antibiotics would be useless, or that sleeping pills might be used in order to take an overdose, the patient is likely to leave the surgery empty-handed.

In addition, in relation to prescription medicines, the medicine is paid for neither by the person who makes the purchasing decision, nor by its ultimate consumer. The vast majority of patients in the United Kingdom pay nothing for their medicines. Prescription charges have been abolished in Wales, Northern Ireland and Scotland, and in England, because children, the elderly and the unemployed are exempt, only a minority of patients actually pay the prescription charge. Even for those English patients who do have to pay £7.40 per prescription, this will commonly be a fraction of the real cost of the drugs, which are funded instead through the NHS budget, and ultimately through general taxation.

Doctors decide which drugs to prescribe, but they do not pay for them. Patients do not decide which drugs they are prescribed, and again, they will rarely pay the full cost. Of course there are other situations when people buy things for others' consumption, but it must be admitted that in the context of prescription drugs, normal market relationships between manufacturers of products and their ultimate consumers are distorted, to say the least. In chapter five, this issue will be revisited in relation to the implications it has for advertising and marketing.

Doctors act as the gatekeepers to prescription medicines, and this is important in relation to the risk-benefit calculation that must be carried out when deciding whether a medicine is safe enough to be licensed for use in patients. If a medicine is effective in curing a very serious condition, but known to cause terrible side effects in some users, doctors should, in theory, be able to ensure that it is prescribed only to people in whom it can be used safely. An extreme example might be the drug thalidomide, which was withdrawn from use after evidence emerged that it caused extremely serious birth defects. In recent years, there have been indications that thalidomide can be effective in the treatment of leprosy and certain cancers. Its side effects mean that it is unthinkable that thalidomide would ever be available 'over-the-counter', but the doctor as intermediary is able to ensure that its use is limited to people who are gravely ill and who are informed in clear and direct terms that they must not expose themselves to even the smallest risk of pregnancy while taking the drug.

Of course, while the prescription system should enable a high level of third-party control over the consumption of medicines, the rise of online pharmacies poses a new challenge to what has been called the 'learned intermediary' rule.[2] If you type 'buy Valium' or 'buy Ritalin' into Google, there is no shortage of sites, frequently based offshore or with no information about their location,[3] offering prescription-only medicines for sale and shipping without a prescription. Indeed, 'buy Viagra without prescription' comes up with 20.9 million hits on Google.

[2] *Sterling Drug v Cornish* (370 F.2d 82, 85) 1966.

[3] TL Bessell et al, 'Quality of Global E-pharmacies: Can we Safeguard Consumers?' (2002) 58 *European Journal of Clinical Pharmacology* 567–72.

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