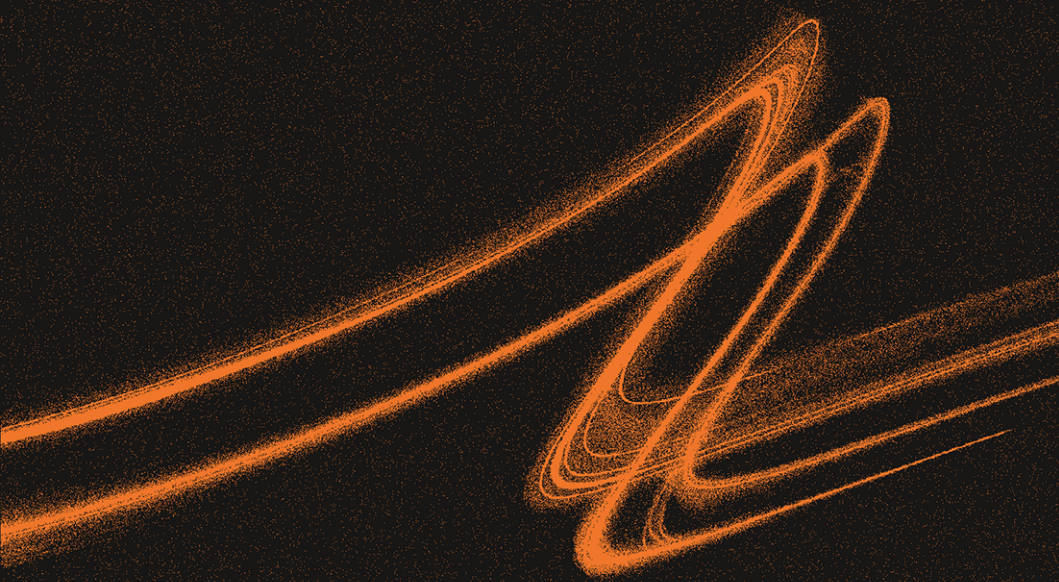
UNHEALTHY PHARMACEUTICAL REGULATION

INNOVATION, POLITICS AND PROMISSORY SCIENCE

COURTNEY DAVIS AND JOHN ABRAHAM



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Unhealthy Pharmaceutical Regulation

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Unhealthy Pharmaceutical Regulation

Innovation, Politics and Promissory Science

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To Cai, Manon and Jess

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Preface and Acknowledgements

Our eight-year long investigation into the regulation of innovative pharmaceuticals in the two largest pharmaceutical markets in the world has taken us many places both in the literal spatial sense and intellectually, from the offices of the world's largest drug regulator just outside Washington DC to the company of consumer advocates lobbying the European Parliament. We have also learned about the workings of a whole range of institutions and drugs, from the FDA and the CHMP to the role of blood-glucose control and heart rhythm in drug evaluation. The perspectives of many disciplines have also needed to be brought to bear on getting to grips with the complexities of pharmaceutical innovation and regulation, such as clinical pharmacology, epidemiology, history of medicines, political economy, political science, science and technology studies, sociology, and toxicology.

This would not have been possible without the generosity of scores of people who have given up their time to be interviewed or helped in other ways with advice or document searches. Our thanks go to all of them for their co-operation and assistance, even if they may not agree with all of our findings, and if many cannot be identified. We are particularly grateful to our former colleague, Tim Reed, for helping with some early parts of the project, and to various colleagues on both sides of the pond for their encouragement over the years, notably, Joe Collier, Graham Dukes, Andrew Herxheimer, Joel Lexchin, Barbara Mintzes, Kenneth Oye, Larry Sasich, Rein Vos and Caroline Wilson, to name but a few. Special thanks go to Andrew Webster and Sally Wyatt, the series editors, for their immense patience and unswerving support for the completion of this lengthy endeavour. We also very much appreciate the sustained commitment to this book project shown by Andrew James and his colleagues at Palgrave. Last, but not least, we are grateful to the UK Economic and Social Research Council (ESRC) for supporting four years of the research underpinning this book, especially most of the international fieldwork, in a way entirely consistent with the important goal of truly independent social science.

List of Abbreviations

AACR	American Association for Cancer Research
ABPI	Association of the British Pharmaceutical Industry
ADOPT	A Diabetes Outcome Progression Trial
ADR	adverse drug reaction
ALLHAT	Antihypertensive and Lipid Lowering to prevent Heart Attack Trial
ASCO	American Society for Clinical Oncology
BfArM	Bundesinstitut fur Arzneimittel und Medizinprodukte
BGA	Bundesgesundheitsamt
CAST	Cardiac Arrhythmia Suppression Trial
CDER	Center for Drug Evaluation and Research (FDA)
CHMP	(EU) Committee for Human Medicinal Products (formerly CPMP)
COMT	catechol-O-methyl transferase
CPI	Critical Path Initiative
CPMP	(EU) Committee for Proprietary Medicinal Products
CSM	(UK) Committee on Safety of Medicines
DDMAC	Division of Drug Marketing and Communications (FDA)
DG	Directorate-General
DHHS	(US) Department of Health and Human Services
DREAM	Diabetes Reduction Assessment with ramipiril and rosiglitazone Medication
DTCA	direct-to-consumer advertising
EBE	European Biopharmaceuticals Enterprises
EFPIA	European Federation of Pharmaceutical Industry Associations
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EORTC	European Organization for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EPPOSI	European Platform for Patients' Organisations, Science and Industry
ERMS	European Risk Management Strategy
EURODIS	European Patient Organization for Rare and Orphan Diseases

FDA	Food and Drug Administration
FDAAA	FDA Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FD&C	Food, Drug and Cosmetic
FOIA	(US) Freedom of Information Act
FR	(US) Federal Register
GAO	(US) Government Accountability Office (formerly General Accounting Office)
GDAC	Gastrointestinal Drugs Advisory Committee (FDA)
GSK	GlaxoSmithKline
HTA	health technology assessment
IBS	irritable bowel syndrome
IBSSHG	Irritable Bowel Syndrome Self-Help Group
IDEAL	Iressa Dose Evaluation in Advanced Lung cancer
IFFGD	International Foundation for Functional Gastro-intestinal Disorders
IFPMA	International Federation of Pharmaceutical Manufacturers' Associations
IMI	Innovative Medicines Initiative
IND	investigational new drug (US)
INTACT	Iressa Non-small-cell lung cancer Trial Assessing Combination Treatment
IoM	(US) NAS's Institute of Medicine
LAG	Lotronex Action Group
MCA	(UK) Medicines Control Agency
MiEF	Medicines in Europe Forum
MPA	Medical Products Agency
NAS	new active substance
NAS	(US) National Academy of Sciences
NBE	new biological entity
NBHW	(Swedish) National Board of Health and Welfare
NCI	(US) National Cancer Institute
NDA	new drug application (US)
NHLBI	(US) National Heart, Lung and Blood Institute
NHS	(UK) National Health Service
NIAID	(US) National Institute of Allergy and Infectious Diseases
NICE	National Institute for Health and Clinical Excellence
NIH	National Institutes of Health
NIHCM	National Institute for Health Care Management
NME	new molecular entity
NORD	(US) National Organization for Rare Diseases

NSC	non-small cell
ODAC	Oncologic Drugs Advisory Committee (FDA)
OTA	US Office of Technology Assessment
PhRMA	(US) Pharmaceutical Research and Manufacturing Association (formerly PMA)
PDUFA	Prescription Drug User Fee Act
PMA	(US) Pharmaceutical Manufacturers' Association
PROactive	PROspective pioglitAzone Clinical Trial in macroVascular Events
RCT	randomized controlled trial
REMS	(US) Risk Evaluation and Mitigation Strategy
SPC	summary of product characteristics (EU 'product label')
TAG	Treatment Action Group
UKPDSG	UK Prospective Diabetes Study Group
US NAS	US National Academy of Sciences
USUDG	US University Diabetes Group

Introduction: The Health of a Political System

Until a few years ago, the political elites in the governments of Europe and North America were pursuing a neo-liberal approach to regulation of the banking industry and the financial sector. What that meant was that there was 'light-touch' regulation and a conviction that by making millions, and even billions, of dollars for themselves, bankers were also delivering good times for the rest of society via tax revenues and the like. The enormous wealth pocketed by some bankers and financiers, we were told, would trickle down to the rest of society. Apparently, wealth creation was the business of the financial sector, so governments should, for the most part, let them get on with it because what the banking industry was doing was in the interests of all of us. This neo-liberal era began in the 1980s on both sides of the Atlantic with New Right politicians, such as Reagan and Thatcher, but was continued under the Clinton and Blair governments, among others.

Neo-liberalism got its name from an emphasis on liberalization of markets, ostensibly to liberate the entrepreneurial spirit of the capitalist and consumer choice from the interference of government regulation. By the late 2000s, a widespread crisis of 'toxic' financial transactions produced an immanent collapse of the international banking system plunging most of the western world into its worst economic recession since the 1930s. The catastrophe for western economies has become so severe that the current generation of young people is thought to be the first since the beginning of the post-war period to have poorer prospects than their parents. It is now widely recognized by governments and political elites of all persuasions that the disaster resulted from inadequate regulation of the banking system and financial sector since the 1980s. In a climate of job losses, falling wages, and austerity in public services, economic growth stalled in the late 2000s in most western countries.

The reaction of most governments and many political commentators has been to call for less regulation of other sectors outside banking in order to stimulate economic growth. But what if the banking industry is not the only sector in which deregulation has produced toxic, and even catastrophic results? One should at least get to grips with answering this question regarding other sectors before embarking on further deregulation. This book is an invitation to start on that journey by exploring the regulation of just one such other sector, namely, the pharmaceutical industry during the neo-liberal era in Europe and the United States (US). While there are many opinions and much commentary about the conduct of pharmaceutical companies, there is far less social science investigation of the reasons for, and consequences of, that conduct.

The pharmaceutical industry is trans-national and vast, with some of its individual products fetching over a billion US dollars on the world market. The industry has prospered during the neo-liberal era. Between 1960 and the early 1980s, prescription drug sales were almost static as a percentage of Gross Domestic Product in western societies. However, from the early 1980s to 2002, prescription drug sales tripled to nearly US$400 billion worldwide, and almost US$200 billion in the US (Abraham 2010, p. 607). Between 2002 and 2006, US prescription drugs sales grew annually by 10 per cent on average, while global sales reached US$600 billion by 2007 (Anon. 2008a). There is no doubt, then, that the drug industry has been able to grow, expanding its sales and profits in the process.

Of course, society's expectation of the pharmaceutical industry is not merely that it makes profits for shareholders and investors. Drug firms' products must also provide some health benefit. The pharmaceutical industry accepts that and contends that its growing sales reflect its success in creating products and innovations needed by patients. For the last 40–50 years (or more in the US and Scandinavian countries) governments have not been so naive as to accept that the pharmaceutical industry's commercial motives will always deliver new drug products in the best interests of patients, so the government drug regulatory agencies check drug companies' claims about their products before permitting them on the market. Yet there is a paradox at the heart of pharmaceutical regulation in the neo-liberal era. On the one hand, state regulation has been introduced and maintained on the assumption that the interests of the pharmaceutical industry and public health do not always converge. On the other hand, the last 30 years has seen a raft of deregulatory reforms, ostensibly to promote pharmaceutical innovation

deemed to be simultaneously in the commercial interests of industry and the health interests of patients.

Drawing on fieldwork-based research in the US and Europe, combined with systematic analysis of a mass of documentary evidence, this book investigates how pharmaceutical regulation has evolved and operated during the neo-liberal era in order to determine whether the deregulatory reforms of that period can reasonably be regarded as being in the interests of public health, or alternatively if, like the banking system, pharmaceutical regulation has been festering in an unhealthy state. To do that we must explore a range of social scientific questions, of which we mention just a few here. Who are the key actors involved and what has been their relative influence on the trajectories of pharmaceutical regulation in the EU and the US over the last 30 years? Can the political convictions of government really determine how the therapeutic efficacy of an individual drug is evaluated? What is the relationship between deregulation, innovation and the availability of valuable therapies for patients? What role is played in shaping regulatory decision-making by public expectations and the assertions of what some scholars call 'promissory science'? Has pharmaceutical regulation and innovation during the neo-liberal era been an unwarranted misadventure or even mis-direction so far as health is concerned, or are they on the right track? It is only within the last decade that the full theoretical and empirical complexities of neo-liberal drug regulation in Europe and North America have become apparent. Based on extensive new international fieldwork and documentary/archival analysis, this book, for the first time, systematically links them together into what may be regarded as the evolution of new a social science discipline concerned with pharmaceuticals and public health policy.

Although this book is a social scientific investigation, it is written for academics and non-academics alike. Academic jargonizing is, therefore, kept to a minimum. While the real world is undoubtedly complex, our view is that the first job of the social scientist is to unravel those complexities systematically and logically, so that they can be explained in a relatively straightforward way. Strong social science should be able to make its case to both non-academic and academic audiences. Similar comments apply to pharmaceutical and clinical science – complex for sure, but, with sufficient effort and inclination, capable of clear explanation to the non-specialist reader. Having said that, we do introduce and develop some social science theories of drug development and regulation, which help the reader focus on the issues at stake in understanding the pharmaceutical sector during the neo-liberal era. The identification

of these theories may be regarded as a way of expressing sets of claims about how the world of pharmaceutical regulation and innovation has operated, so that those claims can be set against evidence in a succinct way in order to build an ever-more accurate and illuminating picture of complex realities. The first chapter begins that task.

1

Putting Pharmaceutical Regulation to the Test: From Historical Description to a Social Science for Public Health

This book examines how innovative pharmaceuticals have been regulated in the US and the European Union (EU) since 1980 – a period which we refer to as the 'neo-liberal era'. Regarding the EU, our principal focus is on the period since 1995 because that is when a supranational EU regulatory agency and system became fully established with specific responsibilities for regulating innovative pharmaceuticals. Like many other writers, we refer to the post-1980 era in the US and western Europe as 'neo-liberal' because it was, and remains, a period in which the political project of minimizing state intervention, subjecting the state to competitive tests of 'the market', and elevating individual consumer choice above the state as a form of collective decision-making, all came to the fore. This has involved the 'liberalization' of markets, that is, relaxation of government regulations and controls believed to hamper business activity and the socio-economic signals of consumer demand (Fisher 2009).

In the US, neo-liberalism found its most committed and enthusiastic expression in the Republican Party's antagonism to 'big government' – a recurrent theme in the rhetoric and often policy objectives of the administrations of Ronald Reagan, George Bush (senior) and George W. Bush. However, the Democratic Administration under Clinton also accepted the political philosophy of 'market liberalization', including the view that the state should help business interests achieve economic success even if that meant retreat from their regulation by government. A similar trend has been evident in western Europe and latterly the EU.

Perhaps the most notorious European enthusiast for neo-liberalism was the UK's Conservative Prime Minister, Margaret Thatcher, who sought to 'free' private industry from state control and regulation – a sentiment deviated from only marginally by the 'New' Labour Governments of Blair and Brown. Until the recent banking crisis of the late 2000s, all of these politicians and governments either actively promoted, or were willing to be persuaded of, the idea that pro-business deregulation was not merely in the commercial interests of industry, but ultimately for the greater good – the 'public interest'.

In the pharmaceutical sector, a raft of pro-business deregulatory reforms ensued during the neo-liberal period (discussed in detail in Chapter 2). They included making the American and European government drug regulatory agencies largely and increasingly dependent on funds from the pharmaceutical industry; increasing the extent and flexibility of consultation between regulators and drug companies; reducing the amount and types of evidence that pharmaceutical firms had to collect to demonstrate the efficacy of particular categories of drugs in order to obtain marketing approval from regulators; and shortening the time taken by government regulatory agencies to grant marketing approval to drug companies for their products. Meanwhile, government regulation of pharmaceuticals maintained its legal responsibility and official democratic mandate to promote and protect public health. In that context, the crucial claim made by government and industry officials regarding the deregulatory reforms was that they would accelerate and increase pharmaceutical innovation, which was in the interests of patients and public health because they needed faster access to innovative drugs. Thus, one theory of pharmaceutical regulation since 1980, which we call 'neo-liberal theory', is that the pro-industry deregulatory reforms of that period were instigated by government in the interests of patients and public health. Implicit in the theory is the proposition that pharmaceutical innovations necessarily promise therapeutic advances for patients.

In this book, we put that theory, among others, to the test by examining both the macro-politics of regulatory change and the micro-sociology of individual drug development and regulation. We present the first social science research to provide an analysis of both American and supranational EU pharmaceutical regulation of innovative prescription drugs. Given that the direction of drug regulation has significant implications for patients, public health and healthcare systems, it is important to understand its socio-political and technical dynamics in order to learn lessons from the past and reflect on possible future policy

options. We wrote this book because it advances those goals substantially beyond the limitations of existing literature.

Previous research on European pharmaceutical regulation is quite modest in extent and is almost always concerned with individual European countries or small groups of such countries. Dukes (1985) conducted an important survey of drug regulation across several different European countries, but it had no specific focus on innovative pharmaceuticals and pre-dated the neo-liberal era and the emergence of a supranational regulatory agency, the European Medicines Evaluation Agency (EMEA) – known as the European Medicines Agency (EMA) since 2010. In their valuable edited collection, Mossialos *et al*. (2004) provide a more recent overview of many different dimensions of pharmaceutical regulation in Europe, but attention to innovative prescription drugs is limited with most coverage ranging widely to pricing, over-the-counter drugs, 'alternative medicines', pharmacies and pharmacogenomics. While Abraham (1995a; 2009) and Daemmrich (2004) examine prescription drug regulation in-depth in the UK and Germany, respectively, by comparison with the US, and Hancher (1989) offers a similar type of comparison of the UK and France, those comparative studies, even combined, provide coverage of only three European countries. More significantly, their analyses are almost entirely confined to events before 1990 and make no attempt to consider supranational EU regulation. Wiktorowicz (2003) provides a more recent comparison of prescription drug regulation in the UK and France by comparison with Canada and the US, taking into account developments in the 1990s, but she also is little concerned with supranational EU regulation and innovative pharmaceuticals *per se*. Only Abraham and Lewis (2000) focus substantially on supranational EU pharmaceutical regulation since 1995, but their analysis is limited to its emergence and early years up to the late 1990s, rather than its effects, and addresses in only a preliminary way the nature of innovative pharmaceuticals within that regulatory system.

Much more has been published about American drug regulation. Temin (1980), Abraham (1995a) and Daemmrich (2004) produced broad analyses of US government control of pharmaceuticals spanning from the late nineteenth century and the origins of the American drug regulatory agency, the Food and Drug Administration (FDA). However, their studies do not stretch beyond the late 1970s or 1980s. Marks (1997) also made an important contribution to the twentieth-century history of US medicines regulation, particularly in relation to standards for drug trials and testing, but his investigation also terminates at 1990. Following in a similar tradition to Marks (1997), Greene (2007) examines post-war

developments in the design, testing and promotion of diabetes and cholesterol drugs, though again the vast bulk of analysis is concerned with events before the 1990s, and most emphasis is given to drug development and marketing, rather than regulation *per se*.

None of those discussions of US drug development and regulation paid much attention to pharmaceutical product innovation within the American regulatory system. It has, however, been the concern of some other scholars. Most notably, Epstein (1996) offers an extensive account of how human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) patients sought to influence the science underpinning pharmaceutical testing and regulation in order to facilitate faster and wider access to innovative AIDS drugs, but his analysis is entirely circumscribed by the HIV/AIDS field. In a quite different approach to pharmaceutical innovation, Angell (2004) examines the extent to which innovative pharmaceuticals across many therapeutic fields owe their origins to industrial research and offer value to patients and healthcare systems. Although the role of drug regulation and the FDA forms part of her discussion, the overwhelming majority of her critique is aimed at the activities of the pharmaceutical industry.

The two main recent analyses of US drug regulation are provided by Hilts (2003) and Carpenter (2010a).[1] Both take a historical approach, which includes retracing twentieth-century regulatory developments before the neo-liberal era. About two-thirds of Hilts (2003) and over three-quarters of Carpenter (2010a) are concerned with events before 1980, also previously investigated by Abraham (1995a), Daemmrich (2004), Marks (1997) and Temin (1980), which need not detain us here. However, the other parts of Hilts (2003) and Carpenter (2010a) make important contributions to any analysis of the FDA in the neo-liberal era, with which we shall certainly engage throughout this book, though only one chapter of Carpenter (2010a) is devoted to neo-liberal influences on the FDA proper. Hilts (2003) emphasizes the impact of 'deregulatory politics' and the New Right' on the FDA after Reagan's election to the presidency, though much of his discussion revolves around controversies over the agency's regulation of food, tobacco and medical devices, rather than drugs. Carpenter's (2010a) focus is fixed on pharmaceutical regulation throughout, but his investigation is less about US drug regulation as such, even less about the relationship between regulation and innovative pharmaceuticals, and much more an account of the organizational dynamics of the FDA within its social and political context. A limitation, therefore, of both Hilts (2003) and Carpenter (2010a) for our purposes of analysing US drug regulation is that they are, in effect,

studies of the FDA. Indeed, Angell (2010) criticizes Carpenter (2010a) for neglecting to consider sufficiently industry influence on the FDA. Carpenter's (2010b) rebuttal accuses her of erroneously misrepresenting him, but also confirms that his investigations lead mainly elsewhere to the question of how the FDA has managed to maintain its power and influence, or found them diminished, in the face of wider neo-liberal politics in the US. Of course, as we embark on our analysis of US *and EU* drug regulation, a more fundamental limitation of all the major works by these American scholars, apart from Daemmrich (2004), is that their examination of pharmaceutical regulation and/or innovation is entirely confined to the US.[2]

Pharmaceutical studies becomes social science

Before 1990, pharmaceutical studies were highly fragmented and could scarcely be regarded as a 'field'. What was available generally took the form of a descriptive history of regulation, policy and/or the pharmaceutical industry, including its criminological activities (Braithwaite 1986; Dukes 1985; Liebenau 1981; Penn 1982; Temin 1980). That began to change with Abraham's (1995a) introduction of theories into the field from political sociology and political science. Most notably ideas put forward by writers, such as Bernstein (1955), Cawson (1986), Middlemas (1979), Miliband (1983), Offe (1973), Stigler (1971) and Wilson (1980), about how social and economic interests influenced governments' decision-making, and the regulatory state, in particular.

For instance, Bernstein (1955), writing from an American perspective, contended that government regulatory agencies, which typically formed in the aftermath of some public disaster associated with industrial activity, initially regulated the industry zealously in the public interest, but gradually over time became captured by the regulated industry, so that it eventually came to regulate primarily in the interests of the industry, rather than the public interest, until another public disaster when the cycle would restart. The school of thought derived from Bernstein's (1955) writings was to become known as 'capture theory'. According to capture theory, regulatory agencies created after some public disaster are given a legal mandate by the Legislature and the Executive arms of the state to regulate an industry in the public interest. When the regulatory agency shifts away from that mission due to capture, it is known as 'administrative drift' or 'bureaucratic drift' because the bureaucratic arm of government (the regulatory agency) has drifted away from the mandate of its Legislative and Executive arms.

Within capture theory, the focus is very much on the relationship between the regulatory agency and the regulated industry. Capture may occur because agency officials or experts, who sit on regulatory agencies' advisory committees, develop attitudes and obligations towards pharmaceutical firms resulting from hospitalities or consultancies. Capture is likely to be increased where informal consultation and meetings between government regulatory officials and industry is permitted and encouraged because the opportunities for regulated firms to lobby government officials are expanded.

One of the most instructive books written about the dynamics of regulatory capture was compiled by Owen and Braeutigam (1978) as a 'how to' manual for industry that recommends techniques with which to manipulate government regulatory official and expert advisers. On lobbying regulatory agencies, they provide the following advice to regulated firms:

> Effective lobbying requires close personal contact between the lobbyists and government officials. Social events are crucial to this strategy. The object is to establish long-term personal relationships transcending any particular issue. Company and industry officials must be 'people' to the agency decision-makers, not just organizational functionaries. A regulatory official contemplating a decision must be led to think of its impact in human terms. Officials will be much less willing to hurt long-time acquaintances than corporations. Of course, there are also important tactical elements of lobbying, of which not the least is information gathering at low levels of the agency staff. Each contact must be carefully tailored to the background and personality of the official being lobbied. For this reason it is useful to keep files on the backgrounds of agency officials. (Owen and Braeutigam 1978, pp. 6–7)

Recognizing that regulatory decisions are often influenced by government agencies' expert advisory committees, firms are also advised to co-opt those experts (often academics), as follows:

> This is most effectively done by identifying the leading experts in each relevant field and hiring them as consultants or advisors, or giving them research grants and the like. This activity requires a modicum of finesse; it must not be too blatant, for the experts themselves must not recognize that they have lost their objectivity and freedom of action. At a minimum, a programme of this kind reduces the threat

> that the leading experts will be available to testify or write against the interests of the regulated firms. (Owen and Braeutigam 1978, p. 7)

Regulatory capture may also occur in a much more passive, structural way, without any lobbying by industry. For instance, the 'revolving door' phenomenon may foster capture. This refers to a subculture within leading organizations in the regulatory process in which officials begin their careers as regulators, but then move on to join the regulated industry; or they begin their careers in industry, then work for some years in the regulatory agency until they are promoted back into the higher echelons of industry. The 'revolving door' can contribute to capture in at least two ways. If regulators have a background of training in industry, then they may be more likely to bring values to the agency which are sympathetic to the regulated industry than if they received training outside industry. More significantly, if regulators view their career development in terms of future promotion into the regulated industry, then they may be unduly concerned to maintain 'friendly relations' with industry at the expense of public interest regulation (Abraham 1995a, p. 73).

In the decades following Bernstein's articulation of capture theory, political scientists, especially in Europe, began to theorize governance and political power in terms of relations between organized interests and the state. By analysing the influence of the trade union movement on UK Labour governments, Middlemas (1979) drew attention to the importance of organized interests in gaining privileged access to the state, above and beyond other interest groups, to the extent that the organized interests governed in partnership with the state, including the delegation of governing powers to those interests in the form of self-regulation. Middlemas (1979) referred to this arrangement as 'corporate bias' and its proposition subsequently became known as 'corporate bias theory'.

Corporate bias theory differs from capture theory particularly because it suggests that regulation and regulatory decision-making needs to be located in a broader political context than solely the relations between regulator and regulatee. Specifically, the wider constituents of the state must be taken into account, not only the 'bureaucracy' (regulatory agencies). The politics of the Executive (the Administration in the US, and the Council of Ministers and national European governments in the EU) and the Legislature (the Congress in the US and the European Parliament in the EU) are also regarded as highly significant in corporate bias theory. For corporate bias theory, the influence of an

organized interest, such as the pharmaceutical industry, may extend to lobbying the top strata of government within the Executive and the Legislature. Representatives of the organized interest may even establish themselves as key advisers to the Executive or sit on high-level joint committees with government Ministers/Secretaries of State setting the policy agenda for regulation of that interest-group/industry. Hence, corporate bias theory allows that a possible mechanism by which industry can drive regulation in its own interests is via the Executive and Legislature without necessarily effecting direct capture of regulatory agencies because the bureaucracy (the regulatory agencies) may be made responsive to industry interests by its constitutional masters in the Executive and Legislature.

Unlike, capture theory, corporate bias theory does not hypothesize a cyclical process of regulatory change. Nor does it postulate that government agencies necessarily begin life with high ambitions to regulate industry vociferously in the public interest. A further difference is that capture theory assumes that pro-industry (de)regulation is associated with the capture phase (of the regulatory cycle) during which the government agency is relatively passive and powerless. By contrast, corporate bias theory allows for the possibility of a relatively strong, pro-active state, which may encourage pro-business (de)regulation in collaboration with industry. Conversely, it follows that corporate bias theory does not assume that the state is zealous in its goals for business regulation only when wishing to regulate strongly in the public interest – an assumption made by capture theory.

After the AIDS crisis, a quite different theoretical perspective from those introduced into discussions of the pharmaceutical sector by Abraham (1995a) began to emerge, especially among American scholars in the aftermath of AIDS patient activism. In particular, Epstein (1996) showed how AIDS treatment activists in the US affected some aspects of new AIDS drug development and regulation. Epstein treated his work as a self-contained ethnography of a social (patient) movement. However, other analysts, such as Daemmrich, Edgar, Krucken and Rothman, read much more into the implications of AIDS patient activism for understanding regulatory change. They took the view that such patient activism had altered drug regulatory philosophy in the US, and that that was part of a wider phenomenon in which changing attitudes of patients, and specifically 'disease-based' patient groups (e.g. cancer or Alzheimer's patient groups) had come to drive regulatory developments and change (Daemmrich 2004; Daemmrich and Krucken 2000; Edgar and Rothman 1990). For instance, Daemmrich writes:

> ... during the 1980s and 1990s ... [t]he American 'patient' evolved from needing state protection from industry and physicians to a free-market consumer who deserved access to still-experimental drugs. As a consequence, FDA placed fewer demands on manufacturers for lengthy testing and redesign of clinical trials than in the past. (2004, p. 81)

Similarly, Carpenter declares:

> Before the 1980s it was rare for the public's attention to be drawn to a drug that the FDA had not approved or was reviewing slowly. The AIDS epidemic changed this ... Yet AIDS was only the beginning of a much larger story of disease-based political mobilization in the United States. To a degree never before witnessed, disease-specific lobbies now press Congress for medical research funding, insurers and state governments for favourable coverage rulings, and the FDA for quick approvals. (2004, p. 57)[3]

On this view, in post-AIDS America at least, drug regulation had become responsive to patient activism and its associated interests. Grander claims implied that a new disease-based politics had taken centre-stage, displacing the old structures of industry interests, on the one hand, and the 'public interest', on the other. This became known as 'disease-politics theory', which added a new dimension to the social scientific nature of the field, and one whose claims are sufficiently clearly articulated to be scrutinized against empirical evidence. We are generalizing this theory to western countries but, in fairness to its proponents, we should point out that they assert it only in relation to the US. Nonetheless, the US is, of course, a major focus of this book.

There can be, what we call, 'hard' and 'soft' versions of disease-politics theory. The 'hard' version is that the new disease-based politics has been in the *interests* of patients and public health; the 'soft' version is that it has resulted from patient activism/demands/pressure, but whether it has been in patients' interests is left open. A variant on the 'soft' version is the idea that US drug regulators have responded to patient activism and media pressure in order to protect their reputation in the public sphere. This reputational theory, which is most associated with Carpenter (2004; 2010a), is essentially instrumentalist because it implies that public image is paramount for regulatory agencies, rather than that they are making decisions in the best interests of public health – though, of course, the two may coincide from time to time. For this reason, Carpenter's

reputational theory does not necessarily claim that regulation is responsive to the health interests of patients, merely to the demands of patient activism in order to preserve the regulatory agency's image of serving patients' interests. He does not, however, take the additional step of attempting to ascertain whether that reputational strategy is *really* in the interests of patients and public health. That may be a result of his methodological constraints. Although the broad institutional and historical sweep of Carpenter (2010a) is very impressive, like Hilts (2003), he does not undertake any in-depth analysis of the techno-scientific basis for regulatory decisions regarding specific drugs, so it may have been difficult for him to comment with confidence on whether regulatory judgements were in the interests of patients and public health.

The techno-scientific aspects of regulation are particularly important when investigating decision-making about innovative pharmaceuticals.[4] In that respect, an important contribution to pharmaceutical studies during the 2000s has been the sociology of expectations applied primarily to technological innovation, especially in the areas of biotechnology and medical technology (Brown and Michael 2003; Brown and Webster 2004; Pollock and Williams 2010). Hedgecoe's (2004) work stands out as an application of this 'expectations theory' to pharmaceuticals, specifically pharmacogenetics. The principal contribution of this theory is the idea that innovations, including pharmaceutical innovations, do not progress in development and/or reach the market solely, or perhaps even primarily, because of compelling techno-scientific logic, but rather because various social actors, such as drug manufacturers or particular laboratory scientists, make promissory claims about the social/health value of the new technology/drug, which create powerful expectations about (and hence demand for) that technology within wider society, including patients. This is what we refer to as 'promissory science'.

In the pharmaceutical sector, 'expectations theory' maps most directly on to drug promotion and marketing. Consequently, it has much in common with another strand of research that also developed during the 2000s, namely studies of pharmaceutical marketing (Applbaum 2007; Fishman 2004; Lakoff 2005; Sismondo 2008). The way in which pharmaceutical companies promote some scientific studies during drug development and recruit medical professionals to act as 'opinion leaders' to support the marketing of new products has been written about for decades (Abraham 1995b; Collier 1989; Relman 1980). Nonetheless, before the 2000s, the overwhelming approach to pharmaceutical marketing was to analyse promotion and advertising of drug products once they had reached the market. The recent studies of pharmaceutical

marketing have given renewed emphasis, and drawn particular attention, to the role of marketing strategies in promoting clinical trial results and even medical conditions, long before an associated drug product actually reaches the market. Those studies can be seen to dovetail with 'expectations theory' because the purpose of such marketing strategies, which amplify promissory science, is to influence how medical professionals, patients and regulators view a forthcoming pharmaceutical.

Expectations theory and marketing studies help to build up a social scientific picture of what may be happening within pharmaceutical innovation and regulation, especially at the interface between industrial science and medical professionals. However, they differ from the other theories we have discussed in this section in a number of respects that point to some limitations in how they have developed to date. Expectations theory tends to concentrate its study on the social *processes* of *early-stage* technological innovations and much less on outcomes, such as regulatory decisions or health outcomes in use. In particular, while identifying how social actors create expectations via various promissory claims about new medical technologies, expectation theorists rarely, if ever, follow through with an analysis of whether or not those promissory claims are valid – and by implication what the truth-value of that promissory science tells us about whether or not the new technologies are in the best interests of patients' health. Similarly, while it is interesting to learn about how transnational pharmaceutical firms go about constructing their marketing strategies, analysts of such marketing rarely engage in any substantive investigation to determine whether such marketing claims are true, and, therefore, whether the claims represent legitimate dissemination of scientific information or commercial bias, together with what then follows for public health.

In addition, pharmaceutical studies focused on industry marketing strategies tend to ignore the regulatory dimension, as if to suggest that understanding the promotional activities of companies is sufficient to explain how new drugs reach markets. However, such a suggestion is mistaken because, no matter how extensive and sophisticated the marketing strategy of a drug company is, the ultimate decision about whether or not a new drug is permitted on to the market rests with the relevant regulatory authority. Hence, the role of regulatory agencies is absolutely crucial to understanding how pharmaceuticals reach the market. While expectations and marketing theory have been a valuable auxiliary to the development of pharmaceutical studies as social science, these limitations have undermined their potential to inform policy.

The emergence of this rich array of theoretical perspectives on pharmaceuticals in society has never been brought together before. We suggest that it represents the beginning of a social science (sub)discipline concerned with the sociology of pharmaceuticals and public policy. That is to say, the scientific study of the socio-political relations of pharmaceutical production, development and consumption. Evidently, our focus in this book is on regulation, innovation and health.

The theoretical and methodological approach of this book

Following Abraham (1995a; 2008), we take an empirical realist, interests-based approach. That is, we presuppose that within regulated capitalism, such as exists in the pharmaceutical sectors of Europe and the US, drug firms have objective commercial interests in maximization of profits for their shareholders and investors, while patients and the wider public have objective health interests in the maximization of the benefit–harm and benefit–risk ratios of pharmaceutical products. The pharmaceutical industry often argues that it is a highly profitable industry because it manufactures products that patients and healthcare systems need, with the implication that the commercial interests of drug companies and the health interests of patients and the public coincide. Sometimes those interests do converge, but as Abraham (2008) has pointed out, the very existence, and historical development, of government intervention to regulate the pharmaceutical industry logically implies that those interests can often diverge or conflict, and that consequently pharmaceutical manufacturers cannot be trusted to be the sole arbiters of whether their products are in the health interests of patients. If drug companies could be so trusted, then the existence of government regulation to check the safety and efficacy of pharmaceutical products would be unjustifiable. Thus, government drug regulatory agencies have been established ostensibly to regulate the pharmaceutical industry in the interests of patients and public health. Moreover, both the EU and US drug regulatory agencies accept that it is their legal responsibility to protect and promote public health.

Like the well-known and centuries-old philosophy known as 'positivism', our realist methodology is committed to the pursuit of truth and the identification of mechanisms and causes to explain objective phenomena. For many readers, this statement may seem like 'common sense', yet it is surprising how many scholars from the late twentieth century onwards have become uncomfortable with, and eschewed, the idea that a crucial role for social scientists is to the discover the truth

about our world. A notable exception is Carpenter, who recently applied a 'positivist' approach to his investigation of the FDA (2010a, p. 28).

Although our realist approach has much in common with positivism, it also differs from it in some important respects. Throughout the ages, one of the hallmarks of positivism has been the conviction that the best way to get at the truth is to (attempt to) adopt a standpoint of 'value-freedom' or 'value-neutrality', except, of course, for a value-commitment to pursue truth itself ((Hammersley 1995; Keat 1981; Weber 1949). This 'neutrality standpoint' has become so pervasive within academic research that it has infected huge areas of social science well beyond positivism.[5] Yet it is misguided, serving more as an academic ideology that mistakes 'neutrality' for objectivity, than a principle of (social) scientific endeavour (Lukes 1973).

Instead of taking the problematic notion of 'neutrality' as our starting point, we apply a modified version of the transcendental philosophy[6] utilized by the realist philosopher of science, Roy Bhaskar (1975), by asking the question: what must the pharmaceutical sector be like in order for its raison d'etre to make sense? This is not an arbitrary, subjective, or utopian question. All parties in the sector, including the pharmaceutical industry, agree, publicly at least, that the intelligibility of producing prescription pharmaceuticals (and other medical drugs) in society is to improve health. While the pharmaceutical industry may fulfil other important socio-economic objectives, such as employment and tax revenues, such objectives are secondary, not least because they could be achieved by expansion of other industries without a pharmaceutical industry. Thus, in order for the existence of the pharmaceutical industry to make sense, its products should improve health. It follows, therefore, that in analysing European and American drug regulation, it would be very strange, and indeed make little sense, to adopt a neutral standpoint about whether such regulation should be in the interests of public health, as that is the ostensible raison d'etre of such regulation. Rather, our pursuit of truth and explanation is informed by an objective[7] value-commitment to determine how well such regulation meets health interests.

Our approach also differs from the historical constructivism of Epstein (1996), Marks (1997) and Daemmrich (2004), and the sociological constructivism to be found in much of expectations theory, which tend to limit analysis to how agents create and act upon their beliefs, networks and goals, falling short of relating such agency to a common framework of objective health interests. While such constructivism can provide some valuable insights, as far as it goes, we contend that

social science and policy analysis needs to incorporate not merely what industry, government, professionals and patient/consumer organizations are doing in 'their worlds', and what their agendas might be, but also how their activities relate to the primary purpose of objective health improvement via drug treatment. Following Lukes' (2005) conceptualization of power, our objectivist realism has the further implication that patients' desires and demands are *not necessarily* consistent with either the interests of public health or even their own health interests because patients *may* lack the requisite power (of, say, comprehensive knowledge) to realize their health interests. Furthermore, within our theoretical framework, a powerful drug regulatory agency is one which protects and promotes the interests of health effectively, given that that is its raison d'etre, rather than merely maintaining its reputation with pertinent audiences – the apparent foundation of Carpenter's (2010a) instrumentalist (not realist) conceptualization of power. While a regulatory agency may establish instrumental power by furthering its reputation with particular audiences, we ask the deeper question: does that instrumental, reputationally based power translate into real power to maximize the interests of public health? Similarly, while a pharmaceutical firm may generate expectations about the therapeutic value of a drug through promissory science, we scrutinize the validity of the claims inherent in those expectations by setting them alongside the techno-scientific data supposed to support them.

We have spent the last eight years investigating these issues with respect to the regulation of innovative pharmaceuticals in the EU and the US in the neo-liberal era. That has included several years of fieldwork in the US and across Europe between 2003 and 2008. Much of our research involved the collection and analysis of documents while in the field and when based at 'home-desks'. Documentary and archival analysis was complemented by some 50 semi-structured interviews, out of 109 sought, with scientists and managers from the pharmaceutical industry, current and former EU and US drug regulators, expert science advisers, relevant legislators and clinical investigators, and representatives of American and European patients' groups, consumer organizations, and public health advocacy bodies. Respondents' requests for anonymity have been respected throughout this book.

We chose to investigate drug regulation in Europe and the US because they are the two largest pharmaceutical markets globally and homes to the two largest and best-resourced regulatory agencies in the world. Japan, the third largest pharmaceutical market in the world is beyond the scope of this book and deserves a separate study. The decision to research both