2
The Political Economy of 'Innovative' Drug Regulation in the Neo-Liberal Era

Introduction

As explained in Chapter 1, the basic legislation governing pharmaceutical regulation in Europe and the US was established by the 1970s. That legislation did not require, as a condition of marketing approval, that new drug products should provide therapeutic advance for patients over drugs already on the market, and nor has it been revised to do so. Nonetheless, other far-reaching institutional, administrative, policy, and legislative reforms concerned with expediting the development, regulatory review, and marketing approval of new drugs have been introduced since 1980. Most of those reforms have been aimed at speeding up patient access to new drugs, product development times, and regulatory review times. European and American governments have justified the reforms on the grounds that they benefit patients and public health by increasing and accelerating new drug innovations that patients need, though, as we show in this chapter, such arguments and rationalizations have rested on a particularly limited conceptualization of patient 'need', namely the need for quicker access to new drugs.

The argument that accelerated drug development and review was a response to patients' demands and interests has been made significantly more widely, and apparently been more persuasive, in the US than in Europe because of the exceptionally active role played by the American AIDS patient movement to expedite access to drug treatment for HIV/AIDS. For instance, upon winning the 1997 'Innovations in American Government Awards Program' in recognition of far-reaching changes to expedite its drug approval process, the FDA (1997a) claimed:

C. Davis et al., *Unhealthy Pharmaceutical Regulation*

> Speeding the delivery of new drugs to Americans, while preserving the FDA's high standards for quality, efficacy, and safety, has always been the primary goal inspiring the drug review program innovations.

This illustrates the way in which the question of how the FDA should respond to the therapeutic needs of patients in relation to its regulation of pharmaceutical products has been framed primarily in terms of speed of access. In fact, the 1997 Food and Drug Administration Modernization Act (FDAMA) created a new mission for the FDA stressing that it should 'promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner' (FDAMA 1997, section 406b).

In attempting to account for this emphasis on speed, some FDA officials contend that the agency was forced to rethink its assumptions about the purpose of drug regulation as a consequence of encounters with the AIDS patient advocacy movement. One FDA official claimed that, before the mid-1980s, the message received by the agency from the US Congress and public was 'that it is better to take more time and be certain, than to move quickly and possibly make a tragic mistake', but following the 1988 demonstrations outside FDA offices by AIDS activists, 'the traditional relationship between FDA, the active protector, and the passive, protected patient, had to change' (Holston 1997).

Another senior FDA official elaborated and rationalized the situation as follows:

> The fundamental debate was: yes, you are a consumer protection agency, but you can protect people to death, and that's what's happening. You've got to live with this tension ... There are some situations where you promote health by protecting people and other situations where you promote health by being a facilitator and making sure they get what they need, and making sure you're not being a roadblock ... And it was *that* piece of the puzzle that the agency had always been blind to. They were so concentrated on [their public health protection role] that they didn't realize they were protecting people to death. And that's really what the HIV population woke this agency up to, philosophically.[1]

As we discussed in Chapter 1, a number of academic scholars, who we call 'disease-politics theorists' have also argued that the demands of patient advocacy groups – and in particular the AIDS advocates – for quicker access to new drugs have driven the procedural and philosophical

changes in US drug regulation which occurred during the 1980s and 1990s (Smith and Kirking 1999; Carpenter 2004; Carpenter and Fendrick 2004; Daemmrich 2004).

In this chapter, we trace how the macro-political landscape of the EU and the US influenced drug regulatory reforms. In so doing, we investigate and explain which actors and institutions were most significant in shaping the orientation of regulation of innovative pharmaceuticals in both regions. In particular, we identify the full range of regulatory reforms introduced since 1980 ostensibly in order to stimulate pharmaceutical innovation by accelerating drug development and marketing approval. The evidence presented compels one to appreciate that drug regulatory reform in the period from 1980 is much more complex than the official view that it should be characterized as quickening delivery of innovative pharmaceuticals needed by patients. Our analysis in this chapter reveals the ideological motivations, material interests, and institutional outcomes of such reforms.

Neo-liberal reforms and corporate bias in European nation-states

The UK election of Prime Minister Margaret Thatcher in 1979 and her New Right Conservative Party in three subsequent elections marked the beginning of the neo-liberal shift. The Thatcher Government was elected with a positive commitment to reduce state intervention in the economy; pharmaceutical regulation was to be no exception. At that time, drug regulation was conducted by a section within the UK government's Department of Health called the Medicines Division, also known as the UK Licensing Authority. During the 1980s, the Association of the British Pharmaceutical Industry (ABPI) badgered the British Government to organize drug regulation more efficiently according to the industry's desire for faster marketing approvals. The Thatcher Administration was already planning reform of the civil service as part of its neo-liberal agenda so it was sympathetic to the pharmaceutical industry's claims that state regulation was insufficiently responsive to the needs of business and innovation because it did not approve new drugs on to the market fast enough (Abraham and Lewis 2000, pp. 60–2). However, an alternative perspective of the situation, rarely heard at the time, was that the Thatcher Government had starved the Medicines Division of resources.

In the ten years to 1986, new drug licence applications of all types had increased by 87 per cent, while staff levels in the Medicines Division grew by only nine per cent. In the late 1980s, the FDA had six times as many staff

handling drug applications as the UK Licensing Authority (Anon. 1989a, p. 3). The Medicines Division may not have been structurally inefficient, but rather under-resourced. Further doubt is cast on this 'inefficiency thesis' by the fact that from 1961 to 1985 more new 'innovative' drugs (NASs), were first marketed in the UK than in Austria, the Benelux countries, Italy, Scandinavia, Spain, Switzerland, the US, or, what was then, 'the Eastern Bloc' of Europe (Andersson 1992, p. 68). Indeed, in 1988, the UK was found to have the fastest approval times for new drugs in the EU, then 'the European Community (EC)' (Anon. 1988a).

Nonetheless, the neo-liberal reforms went ahead. A new regulatory authority, known as the Medicines Control Agency (MCA), was established with a new director, who came from the pharmaceutical industry. The Medicines Division had recouped about 60 per cent of its annual running costs in fees from pharmaceutical firms for regulatory work involved in the licensing process, while 40 per cent came from the Treasury via taxation. By contrast, under the MCA, the entire running costs of UK drug regulation were to become dependent on fees paid by pharmaceutical firms (Anon. 1989b).

Negotiations over the licensing fees laid bare the 'exchange' underpinning the new arrangements. For example, in 1989, the industry objected to paying a licensing fee as large as £50,000 without assurances that their drugs would pass more quickly through the UK regulatory system (Anon. 1989c). On arrival, the new director of the MCA announced that the agency aimed to reduce the net processing times for new drugs by 24 per cent within a year (Anon. 1989a, p. 2). Between 1989 and 1993, new drug processing times fell by more than half, from 154 working days to just 67, while the number of licences granted for new drugs increased from 57 in 1989 to 77 in 1993 – results for which the pharmaceutical firms paid handsomely, making the MCA one of the richest regulatory agencies in Europe (Abraham and Lewis 2000, pp. 65–6). Moreover, the agency increased its consultation with companies and integrated industry interests into its mission statement, which promoted the perspective that the interests of industry and public health coincided:

> Overall, the agency aims to provide an efficient, cost-effective service that protects the users of medicines while not impeding the effectiveness of the pharmaceutical industry. (MCA 1991, p. 1)

Notably, there is no evidence of patient activism or demands for any of these reforms at that time in the UK. Rather, in 1991, the British Government invited the industry to join a board of experts to advise the

Department of Health on the scope of the MCA's targets and performance (Anon. 1991a). Patient activism or even awareness about such matters were so absent that government ministers made little attempt *even to present their reforms as if they were a response to patient demands* (Abraham and Lewis 2000, pp. 64–5).

These neo-liberal reforms in the UK were to be influential on other European countries and the framework for Europeanization of pharmaceutical regulation that ultimately informed the nature of the supranational EU regulatory system established in 1995. For instance, soon after these UK reforms, one can observe similar developments in Sweden and Germany. In both countries, a shift to the political right was taking place, though we are not suggesting that the neo-liberalism of Germany, Sweden, and the UK were identical. Nevertheless, in the context of pharmaceutical regulation, the commonalities were unmistakeable and far outweighed subtle differences.

In the context of the growing power of the political right elected to government in Sweden in 1991, the Swedish Audit Office received relentless complaints from the pharmaceutical industry that drug approval times were too long (Abraham and Lewis 2000, p. 67). They were certainly longer than in many other countries – between 1972 and 1983 NASs came to the market in Sweden slower, on average, than in France, Germany, Italy, the UK, or the US (Andersson 1992, pp. 62 and 68). In response to industry complaints, pharmaceutical regulation was removed from the government's Department of Drugs at the National Board of Health and Welfare (NBHW), in 1990, and taken over by a newly established Medical Products Agency (MPA) to improve 'efficiency'. This changed the political culture of Swedish drug regulation. The MPA derived higher licensing fees from industry on the understanding that the regulatory agency would deliver faster drug approval times, which were indeed cut by more than half between 1989 and 1993, together with increased consultation with pharmaceutical firms. As in the UK, neo-liberal tendencies afforded the pharmaceutical industry more influence over regulatory policy. For example, in response to industry requests, in 1993, the MPA agreed to no longer publish the fact that an application had been rejected, thus denying the public and wider scientific community access to such knowledge (Abraham and Lewis 2000, pp. 68–70). There is no evidence that organized patient activism drove or demanded these changes in Sweden, or even had significant awareness of them.

In Germany too, the election of the neo-liberal Christian-Democrats-led right-wing coalition in the 1980s and 1990s made the Government more responsive to pharmaceutical industry complaints about regulation.

In this period, the pharmaceutical industry consistently pressed the German drug regulatory authority, the Bundesgesundheitsamt (BGA) to accelerate new drug approvals in the administrative courts. In fact, from 1961 to 1985, more new drug innovations (NASs) were first introduced in Germany than nearly any other industrialized country, and between 1972 and 1983 more NASs reached the German market faster than in France, Italy, Sweden, or the US (Andersson 1992, pp. 62 and 68). Senior staff at the BGA blamed the poor quality of many industry applications for the slowness of the regulatory review process. For instance, of the 62 new drugs approved in 1988, only two fell into the BGA's category of outstanding significance (Abraham and Lewis 2000, p. 73).

Nevertheless, against this background of dissatisfaction with the BGA in industry and, in 1993, a public scandal concerning HIV-infected blood transfusions to some 350 haemophiliacs, the German Health Minister, who blamed the BGA for the scandal, vowed to dissolve the agency. In 1994, it was replaced by the Bundesinstitut fur Arzneimittel und Medizinprodukte (BfArM). The BfArM was organized into 'business units', which were to be 'customer-oriented', meaning industry-friendly, and dedicated to quickening drug approval times, which were halved by 1996. The new agency also established extensive mechanisms of consultation with pharmaceutical companies to meet industry needs (Abraham and Lewis 2000, pp. 73–5). As with Sweden and the UK, organized patient groups existed in Germany throughout the 1980s and early 1990s, but there is little evidence that they were active in seeking the regulatory reforms visited upon the BGA and BfArM (Daemmrich and Krucken 2000, pp. 517–18 and 526).

Meanwhile, in France, during the 1980s and early 1990s, a corporatist and co-operative partnership between the government regulatory agencies and the pharmaceutical industry remained dominant. The closed and centralized institutional power of this governing system meant that regulatory decision-making was protected from public scrutiny and other groups, such as consumer or patient organizations (Hancher 1990). Unlike Germany, Sweden, and the UK, there is little evidence of sharp neo-liberal government reforms to drug regulation in France in response to industry demands probably because the corporate bias already in place met with considerable industry satisfaction. The absence of a well-staffed centralized bureaucracy, which led the French regulatory agency to delegate responsibilities to external experts sympathetic to pharmaceutical firms, limited the requirements the agency could impose on the industry (Wiktorowicz 2003, pp. 638, 643 and 646). There is even less evidence of patient activists driving

regulatory reforms in France in this period (Barbot 2006; Callon and Rabeharisoa 2008).

Thus, in four European countries, reforms (or arrangements in the case of France) aimed at ensuring that drug regulation could deliver rapid marketing approval were established during the 1980s and early 1990s. In each case, those reforms (or arrangements) were established in response to industry demands and to accommodate industry interests. Few scholars dispute this account of regulatory change in Western Europe. However, as we have noted, several scholars in the field contend that the situation was quite different in the US, where it is claimed that pharmaceutical development and regulation were transformed by patient activism and demands, especially AIDS patient activism. For some such scholars, that contrast between the US and, at least Germany, if not the rest of Western Europe, is an explicit part of their international comparative thesis (Daemmrich and Krucken 2000; Daemmrich 2004).

The drug lag mythology and early neo-liberal shift in the US

During the 1960s through to the 1980s, the FDA gained the reputation for having among the most stringent drug regulatory standards in the world, along with Norway. In particular, it prevented the sale of many unsafe or ineffective drugs in the US, including some drug disasters, which found their way on to markets in other countries (Abraham 1995a; Abraham and Davis 2005; 2006; 2007). Unimpressed, throughout the 1970s and into the 1990s, the pharmaceutical industry and some researchers, such as the conservative economists from the industry-funded Tufts University Center for the Study of Drug Development (Tufts Centre), persistently accused the FDA of being unnecessarily cautious and bureaucratic about approving NASs. Such 'over-regulation', as they characterized it, resulted, they insisted, in important new drugs reaching markets and patients in the UK and other European countries while remaining under review in the US. The consequent 'drug lag', they argued, delayed American patients' access to important medicines, negatively impacting on their health (Wardell 1974; 1978; Kaitin *et al*. 1989; Kaitin and Brown 1995).

In 1981, the critics of the FDA's supposed 'over-cautious' regulation from industry and conservative 'think-tanks', like the Tufts Centre and the American Enterprise Institute, were boosted by the election of Ronald Reagan as US President. A New Right Republican, he believed in minimal regulatory restrictions on business interests, and began what was to be

a run of 12 years in the White House for the Republicans. Nonetheless, disease-politics theorists, contend that the FDA did not respond to pressure from these quarters, including the Reagan Administration, to accelerate new drug review and approvals until such reforms were also called for by AIDS activists in the late 1980s. For example, Edgar and Rothman (1990) assert that, before the mid-1980s, FDA's 'heavy-handed paternalism' was 'heavily biased in favour of caution' about approving new drugs and denied patients the right to their own risk–benefit calculus about pharmaceuticals. AIDS patient activism, they argue, reversed this. Endorsing that view, Daemmrich and Krucken (2000, pp. 514 and 519) argue:

> Whereas complaints about slow drug approvals in the US had little impact on FDA policies during the 1970s, the aggressive tactics of AIDS activists brought about visible policy outcomes in the 1980s. ... Preventive risk-taking by the FDA was criticized by economists and physicians in the drug lag debate. The setting for risk-taking in regulatory decision-making, however, only changed significantly during the AIDS crisis. Hidden consequences of preventive policies, first articulated by drug lag critics, only became politically salient in the 1980s. Patients now demanded the right to assume medical risks and political responsibility for adverse effects of rapidly approved drugs.

Reinforcing this perspective, Carpenter (2004, p. 52) claims that 'patients, more than pharmaceutical firms, shape the political costs to FDA of delaying drug approval'.

One can see from the writings of Edgar and Rothman (1990) and Daemmrich and Krucken (2000) that they have significantly accepted the premise of the drug lag critics that the FDA was overly cautious in the 1970s and early 1980s, with regard to patients' interests. By implication, therefore, they claim that regulatory reforms to accelerate drug approvals were not only driven by patients' demand, but they also reflected patients' interests because AIDS activists' exposure of the ostensible adverse consequences of FDA's over-cautious approach made the US government recognize the 'legitimacy of demands for more rapid drug approvals', vindicating the drug lag criticisms of the FDA made during the 1970s and 1980s (Daemmrich and Krucken 2000, pp. 512–19). This is what we referred to as 'hard' disease-politics theory in Chapter 1.

While Carpenter (2004; 2010a) subscribes to the theory that AIDS activism drove regulatory reforms to speed drug approval, he is more

neutral, indeed silent, on the question of whether such reforms reflected patients' interests. His thesis is rather that accelerated regulatory review and approval was embraced by the FDA in the face of patients' demands because it was in the reputational interests of the agency not to be seen delaying patients' access to innovative medicines. Within his thesis, it would seem to remain an open question whether or not the FDA's reputational interests map on to patients' health interests, which is why we refereed to it as 'soft' disease-politics theory in Chapter 1.

Yet the validity of the claims made by the drug lag critics is highly questionable. Daniels and Wertheimer (1980) evaluated 198 drug innovations that were commercially available in countries outside the US at the end of 1976 and concluded that only 14 per cent offered a potential therapeutic advance. Later, Schweitzer *et al*. (1996) analysed the approval dates of 34 pharmaceuticals, which were marketed in the G-7 countries plus Switzerland between 1970 and 1988, and were designated by panels of doctors and pharmacists to be very therapeutically significant (at the time of their approval). They found that the FDA approved more of these therapeutically significant drugs before the UK regulatory authorities, and ranked third out of the eight countries in approving the drugs on to the market. Moreover, there is evidence that pharmaceutical firms themselves were, in large part, responsible for delays in FDA drug review times. A study by the US Congress General Accounting Office (GAO) in 1980, investigated 27 new drug applications that had been with the agency for more than three years without an approval/non-approval decision. The GAO concluded that this was because the applications were incomplete – a finding confirmed by the applicant companies themselves (Hilts 2003, p. 277).

While anti-regulation critics seeking less state intervention in the market complained that over-regulation at the FDA stifled pharmaceutical innovation and acted as an obstacle to patients' access to medicines, it was in fact industry's unwillingness to develop 'unprofitable' drugs that explained the lack of innovation for treatment of 'rare' diseases, rather than excessive regulation. Consequently, in 1983, Democrats and Republicans working together in the US Congress felt the need to pass the Orphan Drug Act. This involved the state providing tax and (protectionist) market exclusivity incentives for manufacturers to develop drugs otherwise of limited commercial value because they were for ('rare') diseases affecting less than 200,000 Americans and/or they incurred development costs unrecoverable from sales. The legislation was initially opposed by the US Pharmaceutical Manufacturers' Association (PMA), now known as the Pharmaceutical Research and Manufacturers'

Association (PhRMA), which was loath to admit publicly that private enterprise was failing to meet the needs of those patients (Anon. 1982a) However, pharmaceutical firms soon realized that the Orphan Drug Act was a good deal for them and their institutional commercial interests quickly overcame 'misplaced' ideological embarrassments (Meyers 1997). Notably, the Orphan Drug Act also permitted access to still-experimental drugs, before marketing approval, for patients who could not be satisfactorily treated by available alternative medicines – a provision often wrongly accredited to AIDS patient activism.

Regarding the general claim that the FDA was overcautious in the 1970s and early 1980s, Abraham (1995a) conducted an in-depth analysis of FDA's approval of five new non-steroidal anti-inflammatory drugs in that period. He discovered that none offered any significant therapeutic advance over similar drugs already on the market, such as aspirin and/or ibuprofen. Indeed, it was questionable whether some of them met the FDA's efficacy standards, while all had very significant drawbacks in terms of toxicity. For example, regarding one of the drugs, Suprol (suprofen) the FDA's reviewing medical officer stated in November 1985, just one month before approval, that 'suprofen will be the first drug to be approved [by the FDA] in about ten years that has demonstrated no benefit, efficacy or safety, over aspirin' (cited in Abraham 1995a, p. 237). Subsequently, three of the five drugs (including Suprol) had to be withdrawn from the market on very serious safety grounds, two of which (Oraflex and Zomax) were so deadly that they can reasonably go down in history as drug disasters. By reference to the scientific and regulatory standards of the time, Abraham (1995a) concluded that the FDA *had not been cautious enough in the 1970s and early 1980s*, even though the UK and some other European countries were even less cautious.

Although, the drug lag thesis was largely misleading, it is not true that the FDA did not respond to it.[2] From 1974, the FDA began to classify NDAs according to a drug's therapeutic potential as a way of prioritizing agency resources during the review process. Drugs received an 'A' classification if considered an important therapeutic gain over existing therapies, a 'B' denoted a modest therapeutic gain, and 'C' implied little or no therapeutic gain. These classifications were an attempt to reduce the amount of time the agency took to review 'A' and 'B' rated drugs (FDA Oral History Program 1997). This classification system changed to the current 'priority' or 'standard' review system in 1992, within which the 'A' and 'B' ratings were combined under 'priority' (Anon. 1993d).

The FDA's regulatory response to calls for acceleration of drug approvals, however, took on a whole new flavour and scale after the

Reagan Administration entered the White House in 1981. That same year, the Republicans gained control of the Senate. The nation's shift to the right occurred in the context of a large federal budget deficit and rising inflation – reaching 12 per cent in 1980 (Hilts 2003, p. 210). Simultaneously, according to the US National Academy of Sciences (NAS), the international competitive position of key US industries, such as automobiles, steel, textiles and consumer electronics, had declined and there was 'a clear relative deterioration in the foundations of the pharmaceutical industry's competitive position – the research efforts necessary for discovery and introduction of new patented drugs' (NAS 1983, p. 1). As the New Right within the Republican party believed that the cause of America's economic and industrial decline was federal government interference in the private sector, concerns about 'drug lag' caused by 'excessive regulation' of the pharmaceutical industry were likely to receive a sympathetic hearing from the Reagan Administration, which had declared itself committed to a radical deregulatory agenda (Hilts 2003, pp. 210–11). The Republicans controlled the White House continuously from 1981 to 1993 and the Senate from 1981 to 1987.

In January 1981, just weeks after Reagan's election, the chairman of his health policy advisory group sent the FDA a warning that a 'change of attitude' at the agency towards the drug industry was 'essential', while Joseph Stetler, another member of the group, and a former president of the Pharmaceutical Manufacturers' Association (PMA), told a New York conference that the congressional climate was receptive to proposals that would provide 'regulatory relief' for industry (Anon. 1981a). This was not just empty rhetoric. In July 1981, a Commission on the Federal Drug Approval Process was convened at the behest of the Republican congressman, James Scheuer, and Democrat Al Gore. The Commission's aim was to 'reform and restructure' the FDA because, according to Scheuer:

> regulatory overkill at the FDA has made life-saving new drugs unavailable to American patients for years on end while superfluous tests are run and other needless and costly delays are imposed. Thousands of Americans suffer and die pointlessly while the regulatory machine lumbers on. (quoted from Anon. 1981b)

The Commission's recommendations in 1982 sought reforms to promote more rapid FDA review of new drugs. A year later, the NAS (1983, pp. 81–7) advocated adoption of the Commission's recommendations on the grounds that they would boost innovation.

The similarity in perspective of the New-Right Republicans and the drug lag critics is unmistakeable. In particular, proponents of the drug lag thesis and the New Right implied that faster regulatory reviews were not only in the interests of the pharmaceutical industry, but also in the interests of patients. In this respect, neo-liberalism was not only a political stance to protect the sectional interests of business, it was also an ideological discourse, which sought to fuse in the public mind the commercial interests of industry in product innovation with the needs of patients for therapeutic advance and health. That ideology was frequently articulated by proponents of FDA reform throughout the 1980s – and well before the demands of AIDS activists for quicker access to treatment.

For example, regarding proposals to accelerate the FDA's drug review process, the NAS (1983, p. 86) concluded:

> To the extent that the system is improved, the pharmaceutical industry and therefore the public will gain immeasurably. Equally important, as incentives to invest in new pharmaceutical research are increased, greater gains can be expected in the discovery of new drugs that are effective in reducing the public burden of serious diseases that still remain to be conquered. Thus, the very economic incentives that will help return the U.S. pharmaceutical industry to its former stature will have important public health benefits as well.

While in 1986, the US Health Secretary, Otis Bowen reassured an open meeting of the PMA that 'our aims are your aims' and that 'this Administration will remain committed to working with you for positive change, for competition that promotes innovation in the marketplace and, above all, for better health for the American people' (Anon. 1986a).

Concrete reforms at the FDA followed in the early and mid-1980s, which aimed to reduce regulatory review times and data requirements for all new drugs, not only those that promised significant therapeutic advance. Specifically, changes to the regulations governing NDAs and the testing of new drugs, referred to in the US as investigational new drugs (INDs), were 'accelerated and intensified at the request of' Reagan's Task Force on Regulatory Relief (Federal Register 1985, section 1). Those changes became known as the 'NDA and IND rewrites' of 1985 and 1987, respectively (Federal Register 1985; 1987). They adopted several of the recommendations made by the 1982 Commission on the Federal Drug Approval Process, including: narrowing the scope of the FDA's review of

phase I studies during the IND process; replacement of individual case-report forms with summary presentations of data in NDAs; acceptance of foreign data from countries then with less stringent regulatory standards; and new FDA guidelines allowing closer and more frequent contact between industry and agency staff.

The replacement of individual case-report forms with summary presentations of data in NDAs meant that manufacturers no longer had to provide the FDA with as much detailed evidence about the effects of their drugs during clinical trials, except when patients had died or dropped out of the study. FDA managers keenly predicted that this measure would reduce drug review times by six months (Anon. 1982b) While this might have helped to reduce review times, it also required the regulators to place more trust in pharmaceutical firms' reporting, characterization, and quantification of trial events. As we will see later in this book, that shift in trust has, time and time again, strained even the most generous limits of credibility.

The FDA management's focus on streamlining the drug approval process in this period is further illustrated by the transfer of staff and resources into the drug review divisions, to reduce review times, and out of other departments, even during overall budget cuts at the agency (Anon. 1986b; 1989d). Contrary to the assertions of some FDA officials and academics that it was AIDS patient advocates who forced the agency to reassess its regulatory philosophy, before the AIDS crisis, FDA management was attempting to do just that in the 1985 NDA rewrite by reorienting the agency's goals towards 'facilitating the approval of important new safe and effective therapies' (Federal Register 1985, section 1).

Evidently, such policies filtered down the agency to affect FDA reviewing. One reviewer from the FDA's oncology drugs division testified before Senate that management's 'pressure' to expedite the drug approval process could 'compromise the scientific integrity of reviews' because agency scientists were tempted to ignore deficiencies in NDAs, rather than request additional information from pharmaceutical firms (Anon. 1981c). In addition, a Congressional staffer during the mid-1980s told us:

> There was a premium placed on the numbers of new drugs that were approved on a monthly basis. And there were all these December approvals. So there was pressure back then to be able to say: 'we're approving a lot of drugs'.[3]

Indeed, a Congressional Committee found that 30 per cent of innovative new drugs (NMEs) approved from 1980 to 1985 were approved in

December and over 50 per cent were December approvals in 1985 (US Congress 1987). Subsequently, Carpenter (2010a, p. 532) has shown graphically how the steepest growth in this 'December effect' occurred from the early to late 1980s and then persisted until the mid-1990s. If it is true that a rush of approvals in December is indicative of pressure within the agency to increase the annual number of recorded drug approvals, then it certainly operated throughout the early and mid-1980s before AIDS patient activism.

It is clear, then, that acceleration of new drug review at the FDA was driven by demands from industry and their neo-liberal allies in US government before AIDS patient activism even emerged. Moreover, the Reaganite neo-liberal reforms did not distinguish between innovative pharmaceuticals representing therapeutic advance and those offering *no* therapeutic advantage to patients, let alone drugs needed to treat life-threatening diseases. Indeed, after all the reforms of the Reagan period to quicken drug approvals, the FDA reported that, between 1988 and 1991 inclusive, only 17 per cent of NMEs approved by the agency were judged to offer an important therapeutic advance to patients, while 47 per cent offered little or no therapeutic gain (Anon. 1989e; 1990a; 1991b; 1992a).

AIDS, AZT and accelerating patient access to experimental drugs in the US

The HIV virus that causes AIDS was identified in late 1984, but there were no approved drug treatments for AIDS until 1987 (FDA 2009a). However, this was not due to 'regulatory overkill'. In fact, what is notable about the FDA's response to the AIDS crisis is the speed with which the agency acted to facilitate patient access to early investigational drugs to treat the disease. The first drug to receive marketing approval was zidovudine, more commonly known as AZT. The NDA for AZT was reviewed by the FDA in just three and a half months (FDA 2001a) and approved on the basis of very preliminary data. The evidence for AZT's efficacy was based on only one double-blind, randomized, placebo-controlled phase II trial, involving 281 patients treated for six months, and with incomplete data on optimal dose, optimal duration of therapy, and longer-term adverse events. No phase III studies were required. Instead, a phase IV post-marketing study was agreed (Anon. 1988e; 1989l; Kessler 1989). In addition, all patients, who had been on the trial, including those taking placebo, were put on AZT, and the FDA, together with the company, began to distribute the drug to over 4,800 patients (at least a

third of AIDS victims in the US at that time) on a 'compassionate use' basis – a mechanism that allowed patients access to experimental drugs before marketing approval (FDA 2009b; Hilts 2003, p. 244).

Meanwhile, the FDA was also developing what became known as 'treatment IND' regulations – partly within the IND rewrite and partly in response to the AIDS epidemic (Code of Federal Regulations 1987). In April 1987 the agency first published its proposals for new 'treatment IND' regulations which would allow still-experimental drugs intended to treat life-threatening and serious diseases to be distributed to patients before general marketing at a price charged by manufacturers. The new rules, finally approved later in 1987, applied where (1) there were no comparable or satisfactory therapies or drugs available to treat the condition; (2) the drug was under investigation in adequately controlled studies or awaiting evaluation; and (3) the patients were ineligible for enrolment in clinical trials. The evidence needed for FDA approval of a 'treatment IND' could be sufficient in phase II trials for life-threatening conditions, but would not normally be available before phase III for a 'serious' (but not life-threatening) disease (Kessler 1989, p. 284).

Thus, in the early years of the AIDS epidemic the FDA demonstrated its capacity to act quickly and flexibly in the face of a clear public health emergency. Nevertheless, many patients developed resistance to AZT so there remained a pressing need for new therapies and in October 1988, AIDS patient activists protested outside FDA headquarters, accusing the FDA of 'blocking the delivery of promising therapies to people with AIDS' (Hilts, 2003, p. 249). However, a bitter irony of the early confrontations between the AIDS patient activists and the FDA during 1988 was that there were no new AIDS drug applications for the FDA to hold up at that time. The results of the phase I trial of AZT in combination with a new promising AIDS drug, didanosine (ddC) were not presented until June 1990 (Epstein 1997, p. 694; Feigal 1999, p. 33). By late 1988, manufacturers had developed a small number of drugs to treat the opportunistic infections associated with AIDS, and the agency had approved some of these in addition to authorizing, through use of the new 'treatment IND' regulations, pre-approval distribution of others (Holston 1997; FDA 2005a).

As our earlier discussion of the IND and NDA rewrites demonstrates, the FDA was developing and implementing considerable policy changes that were well underway before the agency was targeted by AIDS patient activism in late 1988. However, it seems clear that the concept behind 'treatment IND' regulations concerning access to drugs

before marketing approval was driven by the epidemiological reality of the AIDS health crisis and, to a lesser extent, associated AIDS patient demand, including that which led to the FDA's 1988 policy allowing US citizens to import unapproved AIDS drugs from abroad in small quantities for personal use (Anon. 1988c). As for the pharmaceutical industry, it was deeply ambivalent about these special AIDS measures, fearing they were diverting too much of the FDA's attention away from accelerating new drug approval more generally (Anon. 1987a). However, once it became clear that the concept behind 'treatment IND' was going ahead at the FDA, the industry began to lobby for these special measures regarding access to AIDS drugs to be formalized and *extended* to other disease categories, as occurred with the final 'treatment IND' regulations.

Turning AZT into deregulation: expediting development and approval of drugs for serious and life-threatening conditions in the US

In July 1988 following a meeting of the President's Task Force on Regulatory Relief, Vice-President George Bush, who headed the task force, urged FDA Commissioner Young to develop regulations to 'speed the availability of new drugs for AIDS and other life-threatening conditions for which adequate therapies are not available' (Anon. 1988d). The outcome of the FDA's consequent deliberations with the PMA, patient groups, and others was the 'Interim rule on Procedures for Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses', also known as 'Subpart E' regulations. These extended the application of the procedures that the agency had used to expedite approval of AZT (Anon. 1988e).

The 1988 'Subpart' E regulations permitted marketing approval of a product for the treatment of life-threatening or severely debilitating diseases on the basis of phase II controlled clinical trials that provided adequate data on the drug's safety and effectiveness. Life-threatening diseases were defined as those with potentially/likely fatal outcomes, while 'severely debilitating diseases were defined as 'conditions that cause major irreversible morbidity' (Federal Register 1988). The FDA's rapid approval of AZT had been an exceptional situation – it was the first, and only drug application to treat a fatal disease reaching epidemic proportions, with 'highly persuasive' phase II data (Kessler 1989, p. 287). To be sure, AIDS patient activists had pressed for these regulations to accelerate approval of further AIDS drugs, but

it is notable that Vice-President Bush's Task Force on Regulatory Relief enthusiastically extended those concerns to other life-threatening conditions, such as cancer, as well. Moreover, the PMA then successfully argued for the extension of expedited development and review not only to other life-threatening illnesses where no alternative treatment existed, but also to 'severely debilitating' diseases, including Alzheimers, osteoporosis, and rheumatoid arthritis (Anon. 1988f). Many types of innovative drugs with potentially large markets now fell within the framework of expedited regulatory review. The pharmaceutical industry's ambivalence about the FDA's response to the AIDS crisis evaporated as companies began to see how the context of AIDS and AIDS patient activism could enhance their longstanding and long-term strategy to accelerate drug regulatory review at the agency (Anon. 1988g).

These new regulations permitted approval based on one 'particularly persuasive multi-centre trial (as occurred with AZT), though the FDA stated that typically two 'entirely independent' studies would be required at Phase II (Anon. 1988f). According to the agency, under Subpart E regulations, the same standards for drug efficacy would be required, but the aim was to 'meet the regular standards earlier' (Anon. 1988h). Yet, there would be less safety data than normal and there would be less information on drugs' optimal therapeutic use. That is implicit in the regulations' acknowledgement of the FDA's 'need to answer remaining questions about risks *and benefits'* when coming to its risk–benefit judgement (Code of Federal Regulations 1988, para 312.84a, emphasis added).

Initially, the FDA proposed that approval under Subpart E would have conditional status, with 'remaining questions' to be answered by the drug company through *compulsory* post-marketing studies. However, the industry opposed both those proposals and they were dropped from the final regulations, though of course 'remaining questions' could be answered via *voluntary* agreements between the agency and company on post-marketing studies (Anon. 1988g). No wonder the PMA was so satisfied. While it is true that the idea behind the 'Subpart E regulations' arose and gained credibility from the AIDS crisis, the main impetus behind their implementation as formal procedures within the regulatory state came from the President's Task Force for Regulatory Relief, which encouraged a context enabling the pharmaceutical industry to shape much of the regulations' substantive content, especially widening applications and making oversight arrangements voluntary (Anon. 1990b).

Surrogate endpoints: AIDS, cancer and opportunistic deregulation

Efforts to reform the FDA by industry and the Republicans under President Bush (senior) continued. By the late 1980s, AIDS activists, industry and some government scientists wanted the FDA to approve new AIDS drugs based on what are known as *non-established surrogate measures* of treatment efficacy that could be assessed earlier in the drug development process (Epstein 1997). In phase III clinical trials the standard scientific method for evaluating a new drug is to measure its effect on an event or symptom that is therapeutically meaningful to patients, known as a clinical endpoint, such as death, loss of vision, organ rejection in transplant patients, pain, or other events reducing quality of life – that is, direct clinical efficacy (Fleming and DeMets 1996). However, where death or morbidity caused by disease progression are typically delayed for many years (e.g. diabetes or heart disease), clinical trials with mortality and morbidity as clinical endpoints may require large numbers of patients, take several years, and be very expensive.

Consequently, stretching back decades before the 1980s, to save time and costs, government scientific and/or regulatory agencies had sometimes approved the efficacy of new drugs based on their effects on *established surrogate* measures of efficacy, that is, laboratory/physical measures that substitute for clinical endpoints. For example, a drug's capacity to lower blood pressure is established (among the medical, scientific, and regulatory communities) as a valid predictor, and hence surrogate measure, of clinical efficacy to prevent strokes. Thus, a trial designed to test the efficacy of a drug to lower blood pressure would be a trial with blood pressure as the surrogate endpoint, without directly investigating the drug treatment's effect on the clinical endpoint, strokes. It is then assumed that the treatment's effect on the surrogate endpoint will predict the treatment's effect on the true clinical outcome. A *non-established* surrogate endpoint is a measure 'reasonably likely' to predict clinical benefit, but not demonstrated to be a valid substitute for clinical endpoints (Code of Federal Regulations 1992, section 314.510).

Clinical trials using surrogate endpoints are in manufacturers' interests because they require fewer patients, have shorter duration, and are cheaper, than trials tracking direct clinical effects. A drug approved on the basis of evidence regarding surrogate endpoints will reach the market faster for both the manufacturer and patients than if approved using clinical endpoints. However, approval of a drug based on an *established* surrogate endpoint is a lower standard of efficacy proof than evidence

of drug effectiveness based directly on clinical endpoints because of the extrapolative uncertainty introduced by having to predict true clinical efficacy from the surrogate measure. Drug approval based on a *non-established* surrogate endpoint is an even lower standard because there is little or no evidence, even correlative evidence, that prediction from surrogate measure to clinical outcome is valid (Fleming and DeMets 1996; Sobel and Furberg 1997).

Nevertheless, in 1989, President Bush established the Committee to Review Approval of New Drugs for Cancer and AIDS, with Dr Louis Lasagna (a long-standing proponent of the drug lag thesis) as Committee Chair. Lasagna immediately announced that the Committee would examine the role of surrogate endpoints in expediting drug approval (Anon. 1989g). Although AIDS patient activists pressed for CD4(T)-cell counts as surrogate endpoints for approval of AIDS drugs, cancer patient activism about such matters was, by contrast, largely absent. It is notable that it was the Bush Administration and industry that drove the extension of concern about surrogate endpoints beyond AIDS to include cancer as well.

In September 1990 the Lasagna Committee recommended that the FDA should approve AIDS and cancer drugs based on the non-established surrogate endpoints of CD4(T)-cell counts and tumour shrinkage, respectively (Anon. 1990c) and AIDS activists – anxious to speed patient access to two promising AIDS drugs in development at that time – lobbied the FDA to accept the Lasagna Committee recommendations (Anon. 1990d). The Lasagna Committee made its recommendation in spite of the fact that several studies published between 1988 and 1990 demonstrated the failure of surrogate endpoints in a number of therapeutic areas to predict the effect of specific treatments on clinical outcomes. Cases of 'surrogate endpoint failure' leading to inappropriate, ineffective or harmful (sometimes deadly) treatment of patients included the use of: encainide and flecainide for cardiac arrythmias (CAST Investigators 1989); quinidine and lidocaine for arrhythmia suppression (Coplan *et al.* 1990; Hine *et al.* 1989; MacMahon *et al.* 1988); calcium channel blockers in acute myocardial infarction and unstable angina (Held *et al.* 1989); and sodium fluoride to treat osteoporosis in post-menopausal women (Riggs *et al.* 1990).

As it turned out, CD4(T)-cell counts proved to be a reasonable surrogate measure of AIDS survival. AIDS patient activism and NIAID may be credited with accelerating its recognition as such, which was in the interests of HIV/AIDS patients' health. However, acceptance of Lasagna's recommendations also meant permitting marketing approval of cancer

drugs based on tumour shrinkage, and the situation with cancer drugs was very different from that with the AIDS drugs even though the Bush Administration and the Lasagna Committee had thrown them together. In the 1970s and early 1980s, the FDA had approved cancer drugs based on tumour response rate (ability to shrink tumours) as a surrogate for prolonged survival. However, there were numerous types of cancer in which tumour shrinkage did not consistently correlate with either increased survival or any other clinical benefit. Consequently, in 1985, the FDA's Oncologic Drugs Advisory Committee (ODAC) recommended that tumour response rate should not be a sole basis for approval of cancer drugs (Johnson *et al.* 2003, p. 1404).

Despite a clear rejection by FDA and its expert oncology advisers that tumour response rate could serve as a surrogate endpoint in a cancer setting, the Lasagna Committee recommended in 1990 that FDA should approve cancer drugs that produced tumour regression/shrinkage in more than 20–30 per cent of patients in phase II trials. Moreover the Committee recommended that more work should be done by FDA, in consultation with other groups, to identify potential surrogate endpoints in other disease settings (Anon. 1990c). This would become a prime site for the generation of promissory science and expectations about innovative pharmaceuticals.

Thus by 1991, considerable political momentum had accumulated to shorten development and review times for drugs to treat life-threatening diseases. Surrogate endpoints provided an obvious means to that end. In addition to the Lasagna Committee recommendations and the demands of the AIDS treatment activists, the White House Council on Competitiveness, headed by Vice-President Quayle, which was committed to the removal of 'regulatory burdens' on US business, also endorsed the idea that non-established surrogate measures of drug efficacy could be a basis for marketing approval. According to Quayle, the Council on Competitiveness operated on two premises: first, that a free market and a competitive economy 'are the best allies of the American people', and second, that 'the less regulation – the less government intrusion into peoples' lives – the better' (Anon. 1991c).

The regulatory outcome of these political pressures was the 1992 Accelerated Approval (Subpart H) regulations. The regulations had been negotiated in November 1991 between the FDA, the Secretary of State for Health, and Quayle's Council, but it was the Council on Competitiveness's proposals that dominated. The FDA wanted marketing approval based on surrogate endpoints after completion of Phase II trials to be restricted to drugs for life-threatening diseases where no alternative

therapy existed (Anon. 1991d). However, following industry intervention, accelerated approval was extended to drugs to treat not only life-threatening or severely debilitating, but also 'serious', illnesses – the formal definition of which included reversible morbidity (Anon. 1991e; Code of Federal Regulations 1992; FDA 1998a, p. 4; Willman 2000a).

According to Jeffrey Nesbit, chief of staff to Commissioner Kessler in 1991, that loosening of the criteria for accelerated approval to include 'serious' illnesses occurred as a direct result of industry lobbying, with little or nothing to do with patient activism or demands:

> The pharmaceutical companies came back and lobbied the agency and the Hill for that word, 'serious'... Their argument was, 'Well, OK, there's AIDS and cancer. But there are drugs [being developed] for Alzheimers. And that's a serious illness'. They started naming other diseases. They began to push that envelope. (cited in Willman 2000a)

A measure of how important this was to the pharmaceutical industry can be gleaned from the comments of a Washington drug industry lawyer and US regulatory specialist, Peter Hutt, who argued that the accelerated approval provisions were the 'big bang' item of the Quayle reform programme and, if the FDA could be made to interpret them broadly, could cut three years from the drug development process – more than all the other reforms combined (Anon. 1991f)

The FDA published the final Accelerated Approval Regulations in the *Federal Register* in December 1992. They permit marketing approval of new drugs intended to treat serious or life-threatening illnesses that appear to provide meaningful therapeutic benefits to patients compared with existing treatments on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is 'reasonably likely' to predict clinical benefit (Code of Federal Regulations 1992). As one senior FDA scientist, Robert Temple, subsequently made clear at an Oncological Drugs Advisory Committee Meeting:

> The accelerated approval rule specifically accepted a lower than usual standard. Usually you are supposed to show that there is clinical benefit or have a surrogate that everybody believes is fully acceptable. [The accelerated approval rule] said we can use surrogates that are not of that quality that are more iffy than that, for a particular reason to serve an unmet medical need. (ODAC 2003, p. 80)

Since the true effect on morbidity and mortality of products granted this type of accelerated approval was unknown, manufacturers were required, under the regulations, to conduct 'adequate and well-controlled post-marketing (phase IV) studies to validate the surrogate endpoint or otherwise confirm the effect on the clinical endpoint'. Section 506(b)(3) of the existing 1938 Food, Drug and Cosmetic Act provided for expedited withdrawal of marketing approval by the FDA if: (1) the company failed to conduct the required post-marketing studies with 'due diligence'; (2) post-marketing studies failed to verify clinical benefit of the product; (3) other evidence demonstrated that the fast-tracked product was not safe or effective under conditions of use; or (4) the firm disseminated false or misleading promotional material about the product.

When Reagan was first elected to the White House, American neo-liberalism was largely confined to the New Right in the Republican Party. However, by the time Clinton became President in 1992, neo-liberalism was no longer the sole preserve of the Republicans – even if Democrats tolerated as much as embraced it. Indeed, the two Clinton Administrations of the 1990s did not reverse any of the major regulatory policy shifts instigated during the Reagan and Bush (senior) era. Instead the new 'third way' agenda of the Party's leadership was in many respects characterized by an approach to business regulation and government 'reform' that was consistent with the assumptions and ideology of neo-liberalism. Consider the initial reluctance of the FDA's oncology division to approve cancer drugs under subpart H due to disagreement among oncologists about which surrogate endpoints were appropriate (Clinton and Gore 1996, p. 3). Once again, there is little evidence that pressure for the FDA to accept tumour shrinkage as a surrogate endpoint in cancer trials came from patient advocates (Anglin 1997, pp. 1407–9). Rather, the Clinton Administration's 'Reinventing Government' initiative was decisive, within which President Clinton and Vice-President Gore directed the FDA to accept tumour shrinkage as a valid surrogate marker for accelerated approval (Clinton and Gore 1996). The principal explicit goal of the 'Reinventing Government' initiative was to cut regulatory 'red-tape' for the benefit of business.

The neo-liberal model of resourcing regulation hits the FDA: the Prescription Drug Users Fee Act (PDUFA)

As we have noted, prior to the AIDS crisis, and well before AIDS patient activists protested against the FDA in late 1988, the pharmaceutical industry and its neo-liberal allies in the Reagan Administration and the

Senate sought reforms to reduce regulatory review times for *all types of drug innovations*, irrespective of whether they were to treat serious or life-threatening illnesses, or judged to promise therapeutic advance. It would be wrong to say that the AIDS crisis was a side show so far as that reform programme was concerned, because the challenge of AIDS treatment affected the shaping of some of those reforms, as we have seen. Nonetheless, the neo-liberal reform of pharmaceutical regulation more generally continued throughout the debate about accelerated access to, and approval for, new drugs to treat serious or life-threatening conditions.

As FDA management attempted to decrease regulatory review times across the board, in response to the Reagan government's demands, it did so in a context of severe cuts to its budget, which was provided and set by Congress. Agency staff numbers were reduced from 8,200 in 1979 to just over 7,000 in 1987. Over the same period Congress had passed 20 new laws giving the FDA new responsibilities in both the food and drug area (Anon. 1989i). The FDA budget continued to be suppressed during the Bush (senior) Administration (Hilts 2003, p. 255).

While warning the Reagan and Bush Administrations that the FDA's lack of resources threatened its efforts to expedite new drug development and review, FDA Commissioner Young nevertheless attempted to keep reductions in the agency's drug review times on track by increasing NDA staff at the expense of other (already overstretched) parts of the agency (Anon. 1986b; 1989i) Consequently, other FDA regulatory activities, such as enforcement, were drastically scaled back. The number of seizures, injunctions and prosecutions undertaken by the agency dropped from 500 in 1980 to 173 in 1989 and, according to Hilts, by 1990 the FDA was 'an organizational disaster waiting to happen':

> The industries the FDA regulated were booming. The number of applications for approval of drugs, devices and other products shot up from 4,200 in 1970 to 12,800 in 1989. Over the same period, the reports of serious reactions to drugs increased from about 12,000 to 70,000 per year, not including the 16,000 reports of problems with medical devices, for which the FDA was now responsible. In 1970 the Freedom of Information Act (FOIA) did not exist [or had barely got off the ground at the FDA]; by 1989, as a result of its passage [in 1967], the FDA was fielding 70,000 consumer enquires, 40,000 FOIA requests, 3,000 queries from members of Congress, and 180 citizens petitions for action. In the decade between 1980 and 1990 alone, Congress passed twenty-four laws giving the FDA new responsibilities

> and requiring diversion of at least 675 staffers from other tasks. And the AIDS crisis forced the agency to divert 400 people to deal with it, from blood transfusion issues to the testing of viral drugs. (Hilts 2003, p. 255)

Remarkably, the agency had managed to reduce its average new drug approval times from 33 months in 1987 to 19 in 1992 (US GAO 1995, p. 4). However, since the late 1980s, Vice-President Quayle's industry-friendly Competitiveness Council had demanded that drug review times should be reduced to 12 months (Anon. 1991g). The FDA responded by arguing that lack of staff made that target impossible (Anon. 1990e). A growing awareness that the FDA was inadequately resourced emerged in Congress and beyond. The idea of charging the pharmaceutical industry fees for the FDA's drug regulatory work had been suggested as a solution to the agency's funding problems from the mid-1980s by both the Bush and Reagan Administrations but had never been authorized by Congress (Anon. 1991h). In August 1992, the PMA indicated publicly that it would not oppose fee charges on condition that the fees, which became known as 'user fees', were wholly concentrated on new drug review and, that the FDA undertook to implement 'specific improvements' in the regulatory review process (Anon. 1992b). Later that year, Congress enacted the 1992 Prescription Drug User Fee Act (PDUFA).

The new PDUFA legislation authorized the FDA to collect fees from pharmaceutical firms for each NDA, together with an annual fee for each product on the market and each manufacturing plant in operation. In 1993, it was estimated that over the next five years companies would pay over US$300 million in user fees enabling the FDA to hire an additional 600 staff to review new drug applications (Anon. 1993a) However, in order to collect and spend user fees under PDUFA, each year the FDA had to spend from its Congressional annual appropriations at least as much on the drug review process as it had spent in 1992 (adjusted for inflation). The Act stipulated that user fees could only to be used to fund the drug review process (US GAO 2002, p. 7).

In return for user fees, the FDA agreed to meet increasingly demanding review performance goals regarding all innovative pharmaceuticals, irrespective of whether they offered therapeutic advance. For example, that by 1997 it would review 90 per cent of applications for new products given a standard review classification within 12 months and 90 percent of those accorded priority review status within 6 months (FDA 1997b). Such timeframes were goals rather than deadlines, however the particular character of the user fee legislation meant that FDA was under pressure

to treat the timeframes as deadlines. PDUFA contained a 'sunset' provision whereby the user fee legislation had to be renegotiated every five years, allowing the pharmaceutical industry to refuse continued user fee funding if it felt that the FDA was not fulfilling its obligations under the legislation, or if industry and Congress could no longer agree on specific performance goals. Thus in the US, receipt of user fees became, in effect, conditional upon negotiated performance measures dictated by Congress and the regulated industry. The implicit threat by industry to terminate user-fee funding embedded in PDUFA, in the context of a government (Executive and Legislature) no longer willing to fully fund the FDA, acted as a lever forcing the agency to comply with the performance goals. It also allowed industry considerable *de facto* influence over FDA priorities and policies.

In fact, PDUFA has been re-authorized every five years (known as PDUFA II in 1997, PDUFA III in 2002, and PDUFA IV in 2007) and the FDA has become increasingly dependent on revenues from user fees which had grown to fund over 40 per cent of the total costs of the agency's new drug review activities by 2000 (Federal Register 2000, p. 47994). Under PDUFA II, the agency agreed to year-on-year improvements until 2002 when the goal was to review 90 per cent of standard NDAs within ten months. PDUFA II also added procedural goals requiring the FDA to: respond to industry requests for meetings; meet with industry; provide industry with meeting minutes; and resolve major disputes appealed by industry (FDA 2011a). Those new performance goals were explicitly intended to increase FDA's responsiveness to, and communication with, companies during drug development (Kaitin and Di Masi 2000).

As a result of user fees and the associated increase in FDA staff numbers, new drug review times did indeed decline. FDA review times (not including the time taken by companies to respond to queries by the authorities) for priority and standard NMEs more than halved between 1992 and 2008 – from 13.9 to 6 months, and from 27.2 to 13 months, respectively (see Table 2.1).

According to a study by the US GAO (1995, p. 11), by 1994 the 'drug lag', insofar as it ever existed, was starting to reverse, with UK approval times lagging behind those of the US. For the 12-year period ending 30 September 1994, the UK Medicines Control Agency (MCA) reported that median approval time for applications for new active substances (NASs) was 30 months, while the FDA's median approval times for NMEs in 1994 was 18 months. In 1988, only 4 per cent of new drugs introduced onto the world market were first approved by the FDA. By 1998, 66 per cent of the new products entering the market had received their

Table 2.1 CDER approval times for priority and standard NMEs and new BLAs calendar years 1993–2008

	Priority			Standard		
Year	Number approved	Median FDA review time (months	Median total approval time (months)	Number approved	Median FDA review time (months)	Median total approval time (months)
1993	13	13.9	14.9	12	27.2	27.2
1994	12	13.9	14.0	9	22.2	23.7
1995	10	7.9	7.9	19	15.9	17.8
1996	18	7.7	9.6	35	14.6	15.1
1997	9	6.4	6.7	30	14.4	15.0
1998	16	6.2	6.2	14	12.3	13.4
1999	19	6.3	6.9	16	14.0	16.3
2000	9	6.0	6.0	18	15.4	19.9
2001	7	6.0	6.0	17	15.7	19.0
2002	7	13.8	16.3	10	12.5	15.9
2003	9	6.7	6.7	12	13.8	23.1
2004*	21	6.0	6.0	15	16.0	24.7
2005*	15	6.0	6.0	5	15.8	23.0
2006*	10	6.0	6.0	12	12.5	13.7
2007*	8	6.0	6.0	10	12.9	12.9
2008*	9	6.0	6.0	15	13.0	13.0

*Beginning in 2004, figures include BLAs.

Source: FDA. Available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/UCM123959.pdf (Accessed 15 October 2011).

first approval by the agency (Willman 2000a). As well as reviewing new drug applications more quickly, the FDA also began to approve a higher percentage of them than before. Before PDUFA, the agency approved around 60 percent of all applications submitted, but by 2000, that figure had risen to about 80 percent (Federal Register 2000, p. 47994).

PDUFA formalized and significantly accentuated the neo-liberal agenda of measuring the FDA's performance in terms of the speed with which new drugs were approved on to the market. Supporters of this agenda, including FDA managers required to implement it, asserted that it was progressive for health because the 'consumer' received 'more products, more quickly' (Federal Register 2000, p. 47994). However, it follows from the distinction between pharmaceutical innovation and therapeutic advance, explained in Chapter 1, that faster marketing

approval only benefits patients and public health if the risk–benefit profiles of the new drugs placed on the market sooner represent an advance over drugs already available. Moreover, even if this is the case, there must also be enough scientific data on the drugs' advantageous risk–benefit profiles to allow realization of optimal use by patients and physicians, and those benefits must not be outweighed by public health 'dis-benefits' produced indirectly by PDUFA – for example, a decline in the proportion of funding available for post-marketing safety surveillance activities.

Although the neo-liberal reformers and those in the FDA management, who had resigned themselves to the ideology of their political masters, sought to represent the definition of FDA performance evaluation as speed of approval as good for patients and consumers, some patient/consumer organizations were not convinced. In evidence to FDA public meetings on PDUFA, the American National Organization for Rare Diseases (NORD) commented:

> We believe the overriding success of the agency must be measured not by the speed of its work, but by the completeness and scientific soundness of its work in order to protect the health and welfare of the American public. (Diane Dorman, NORD cited in FDA 2001b, p. 174)

While, the US Center for Medical Consumers remarked poignantly:

> Speedier drug approval clearly benefits industry; in some cases it may benefit patients or specific populations, but in most cases there is no such evidence. It is, therefore, inappropriate for the agency to so narrowly define the objective of PDUFA ... Its self-evaluation and how it defines performance measures should focus on how well its activities improve the well-being of those who are sick and disabled. (Arthur Levin, Center for Medical Consumers cited in FDA 2000a)

Regarding policies pertaining to 'standard' NDAs, patient and consumer groups complained that there was no public health justification for the stringent review timeframes for such drugs as they offer little or no therapeutic advantage. Yet, when PDUFA was re-authorized as PDUFA II in 1997, the review timeframe for 'priority' drugs remained unchanged, but the goal for 'standard' drug review time was reduced from 12 to 10 months. Patient and consumer groups were concerned that, with agency resources stretched, stringent review-time goals for 'standard' (probably 'me-too') drugs forced the FDA to devote

inadequate resources to review drugs that are important to public health. Moreover, they pointed out that, even in relation to drugs for life-threatening or serious diseases where no therapeutic alternatives exist, FDA reviewers should have the flexibility to exercise some scientific judgement on whether the nature and complexity of the data present demanded a longer review time than that allowed by the agency's performance goals (Travis Plunkett, Consumer Federation of America cited in FDA 2001c, p. 26).

These comments by patient and consumer organizations highlight the potential divergence between the interests of public health and the neo-liberal reform programme, which sought to define the FDA's performance solely in terms of speed of marketing approval. The New Right, who advocated the virtues of 'free markets' with limited state regulation of business, entrepreneurship, and associated innovation, promoted this ideology as convergent with consumers' interests. However, such promotion should not be mistaken for fact or even acceptance by patient and consumer organizations. Scholars and other commentators on pharmaceutical policy, who argue that the acceleration of access to AIDS drugs for patients was indicative of a more general shift in American culture towards a desire for faster and more risky pharmaceutical products with less protection by state regulation, appear to have made just that mistake. They have reported an ideological framing of patients' interests by the neo-liberal reformers in government as if it were reality. The responses of patient and consumer advocates to PDUFA provide further evidence that the AIDS drug scenario was an exception in a sea of regulatory reform designed to assist business and industry, with the interests of patients and public health a residual concern. In this respect, a debate that arose in 1994 in the context of a GAO investigation into FDA performance measures under PDUFA is telling. The pharmaceutical trade press, *Scrip*, reported the debate as follows:

> In the belief that the ultimate aim of the 1992 Prescription Drug User Fee Act is to improve public health by enabling patients to receive new drugs sooner, Representative Edolphus Towns, chairman of the US House government operations/intergovernmental relations subcommittee, has questioned whether the data to be collected under the act will be sufficient to determine how far it is achieving this goal. The Department of Health and Human Services, however, has stated that the main purpose of the Act is to find FDA the resources to review applications within certain time frames and thus the programme should be evaluated on the basis of whether the FDA is successful

> in accelerating its review, not on a specific improvement in public health ... DHHS [pointed out] first, that evaluation of improvement in public health 'requires a complex multi-factorial analysis' that goes beyond an assessment of whether new drugs are reaching the public earlier, and second that '*the main aims of [PDUFA] are to give the FDA the necessary resources to review applications within specified time frames and allow drug sponsors [firms] to predict more accurately when product reviews will be completed*'. (Anon. 1994a, emphasis added)

There is evidence to suggest that PDUFA and associated political shifts in the nature of the relationship between the FDA and industry towards one of 'collaboration' in the drug development process have affected the culture of drug regulation within the agency. According to FDA management, the agency agreed to expand its performance goals without requesting additional user fees because it assumed that there would be a consistent increase in the number of NDAs received by the agency between 1997 and 2002 providing sufficient fees to cover the added workload (FDA 2001c, pp. 142–3). Instead the number of NDAs fell (FDA 2004). Hence, the costs of PDUFA commitments exceeded the fees collected resulting in significant increases in FDA reviewers' workload (FDA 2001b, p. 7; KPMG Consulting 2002; US GAO 2002). Between 1999 and 2001, FDA reviewers scheduled nearly 4,000 meetings with pharmaceutical firms under PDUFA II obligations. According to the FDA, a typical meeting could involve 17 reviewers, and the time requirements for a meeting involving all FDA review disciplines could range from about 125 to 545 hours per meeting (US GAO 2002, p. 20).

An investigation by the Inspector General of the US Department of Health and Human Services (DHHS) (2003) also found evidence that increased workload and inflexible PDUFA timeframes might be undermining the integrity of the review process. Forty percent of the FDA reviewers responding to the study, who had been at FDA at least five years, indicated to the investigation that the review process had worsened during their tenure in terms of allowing for in-depth, science-based reviews, while 58 percent thought that the six-month review timeframe for priority NDAs was an inadequate period of time in which to conduct sufficiently substantive, science-based reviews.

Aside from altering the drug review process, PDUFA affected other FDA activities. As PDUFA required the agency to spend a large, inflation-adjusted, amount each year from its annual appropriations on drug approval activities in order to collect user fees, when appropriations from Congress were limited, FDA officials had to reduce resources spent on

other activities to ensure that enough appropriated funds were spent on the review process to enable collection of user fees. By 2000, non-drug-review programmes had to be cut by US$234 million to cover mandatory pay increases, and to ensure that sufficient appropriated funds were funnelled into the drug review process (FDA 2000a). The FDA's workforce and resources for programs other than PDUFA contracted each year from 1992 to 2000 (Federal Register 2000, p. 47994). Thus, the dramatic decreases in approval times were bought at the expense of post-marketing monitoring of adverse drug reactions, tracking of manufacturers' phase IV study commitments, oversight of post-launch advertising campaigns by drug companies, and inspections of industry facilities and conduct (FDA 2000a; FDA, 2001c; Public Citizen 2002; US GAO 2002).[4,5,6]

In 1992, funds obligated for new drug review constituted 17 per cent of the FDA's total budget. By 2000 this figure had increased to 29 per cent. This change was reflected in the distribution of agency staff. In 1993, 14 per cent of full-time employees, or 'full-time equivalents' (FTEs), were dedicated to new drugs review. By 2000, it was 26 per cent. Conversely, the percentage of FTEs employed on other FDA activities dropped from 86 to 74 per cent over the same period (US GAO 2002, pp. 14–18). The activities that were 'down-sized' were important for protecting public health and safety.

Reduction in the funds for key FDA activities after PDUFA is all the more remarkable when we consider that resources for those activities had *already* been severely reduced due to budget cuts and prioritization of the drug review divisions during the 1980s. An FDA needs-assessment study conducted by the agency's Office of Planning and Evaluation in 1991 estimated that the FDA would need to double its workforce between 1991 and 1997 in order to meet its regulatory responsibilities. The study indicated that more staff was needed to boost activities in a number of areas – not only in the review divisions. For instance, during the 1980s, the number of compliance staff at the FDA fell by 30 per cent. Consequently, in 1989, the agency conducted 35 per cent fewer inspections than in 1980 (Anon. 1991i) By 2010, the US DHHS Office of Inspector General reported that only 0.7 per cent of foreign clinical trial sites were inspected by the FDA, while the figure for American sites was just 1.9 per cent (Anon. 2010a). Despite this demonstrated need for *more staff* across all FDA activities, there has been a *decrease* under PDUFA – not only in the proportion, but also in the absolute number, of FTEs working on non-drug-review activities, such as enforcement and surveillance. Between 1992 and

2000, the number of FTEs working on non-drug-review activities fell from 7736 to 6571.

By the FDA's own admission, after PDUFA, post-market drug safety regulation became particularly underfunded, and 'severely challenged' with 'critical new drug safety work…not getting needed funding' (cited in NORD 2002). PDUFA 'stressed' the agency's system for monitoring adverse drug reactions directly, because of the need to prioritize the review process, and indirectly because more drugs entered the US market in absolute terms than before. Also, more drugs than previously reached US patients before patients in other countries. Accordingly, American patients became more likely to be the first exposed to the risks of new drugs placing greater demands on the agency's post-marketing surveillance systems without commensurate resources (FDA 2001c, pp. 65–7). Following an unprecedented number of withdrawals of prescription drugs from the US market on safety grounds in the mid-to-late 1990s and increasing public concern that the FDA was approving unsafe products, the FDA convened open meetings in 2000 and 2001 to discuss PDUFA (Friedman *et al*. 1999; Willman 2000b). Announcing the 2000 meeting in the *Federal Register*, the agency management admitted:

> We are increasingly concerned that spending enough appropriations on the drug review process to meet the statutory conditions [of PDUFA] makes FDA less able to manage the resources available in a way that best protects the public health and merits public confidence. Just one example of an area we have not been able to fund adequately is responding to reports of adverse events related to the use of prescription drugs. (Federal Register 2000, p. 47994)

Subsequently, Congress, the FDA, and the pharmaceutical industry agreed that some user fees could be collected for 'post-approval risk management activities' under the 2002 PDUFA III re-authorization (FDA 2009c). However, objectives to protect public health, as defined by the FDA, in these tripartite negotiations were severely compromised. Under PDUFA III, user fees could be spent on 'collecting, developing, and reviewing safety information' and adverse event reports, but only for drugs approved after October 2002, and typically only for up to two years after marketing approval – three years for drugs considered particularly dangerous (FDA 2005b). Those limitations made it highly questionable that the PDUFA III agreement could adequately meet the drug safety and public health concerns raised by FDA management since research had demonstrated that half of all drug safety withdrawals in the

US occurred *after* the first two years of marketing, and that half of the major drug safety labelling changes occurred after the first *seven* years of marketing (Lasser *et al*. 2002).

Moreover, virtually all of the FDA Office of Drug Safety's proposals that user fees should be spent to supplement the passive adverse events reporting system with a number of pilot projects for active surveillance 'failed to make it past industry-FDA negotiations' for PDUFA III (Patient and Consumer Coalition 2002, p. 1). The increase in funding for drug safety regulatory activities under PDUFA III amounted to US$2.2 million for drug safety, but fell well short of the US$100 million that FDA officials claimed was needed for the agency to undertake proper post-marketing surveillance (NORD 2000).

The process established for negotiating PDUFA and its subsequent re-authorizations enabled the pharmaceutical industry to bargain for specific performance goals prioritizing speed of new drug review and responsive interactions with industry in exchange for FDA funding. As we have seen, that skewed the agency's regulation towards activities that were in the commercial interests of industry – sometimes coinciding with patients' interests, but at the expense of activities that were primarily or solely in the interests of public health. The extent of such industry influence was accentuated by the exclusion of patient and public health organizations from the PDUFA negotiations (FDA 2000a; 2001c). As one former patient advocate recounted:

> The point is that they had cut the deal at the table, excluding people like us. And so the essential deal, about how much money and how to use it, it was cut behind closed doors between the FDA and industry ... These were deals largely done out of the earshot of patient and consumer groups.[7]

For PDUFAs I, II and III, patient organizations and public health advocacy groups were merely asked to comment on measures already agreed between industry, the FDA, and Congress – an unsatisfactory state of affairs that did not go unnoticed according to consumer organizations:

> But the complaint generally is ... that the public is invited in to comment late in the game when things are already fairly well formed and that puts the advocates at an unfair advantage. Not only do we have less money and less influence and less power to influence decisions but, if things have pretty well formed, it's really hard to change them in any substantive way.[6]

As a consequence of complaints by patient and consumer advocates about their exclusion from participation, a commitment to consult with patient groups from the beginning of the negotiations for PDUFA IV was written into the PDUFA III agreement.[8]

What is particularly revealing about our analysis of PDUFA is that when one moves away from the rather exceptional context of AIDS treatment to US pharmaceutical regulation more generally, one finds that, since 1992, for 15 years or more, patient and consumer health advocates were effectively excluded from the consultative role that industry was accorded in shaping the FDA's goals and priorities.[5] Patients, consumers, and associated organizations did not drive or demand PDUFA. Political and economic interests of government and industry drove the PDUFA processes, which profoundly altered American drug regulation and the FDA. Disease politics, though present at times, seems only marginally relevant to this highly significant chapter in contemporary American pharmaceutical policy.

The creation of supranational EU pharmaceutical regulation

Meanwhile, the Europeanization of pharmaceutical regulation across western European nation-states was gathering pace like never before. The transnational research-based pharmaceutical industry saw advantages in the Europeanization project if it harmonized regulatory standards across Europe in ways conducive to greater market access for drug products. Reflecting those transnational priorities, in 1978, the industry established the European Federation of Pharmaceutical Industry Associations (EFPIA), which was a conglomerate of the national industry associations in Europe, and became the official representative of the European industry in negotiations with the European Commission and Parliament. In theory, at least, increased European harmonization of regulatory standards could mean faster access to a transnational, if not pan-, European market. Conversely, separate and distinct national regulatory regimes, with different technical standards and divergent safety regulations tended to add to the costs of transnational firms. Thus, industry interests converged with those of the European Commission and Europhiles in national governments and the European Parliament, who were committed to European integration.

In 1988, a Commission report on the 'Single European Market' (successor of the ' Common Market') accepted the argument put forward by EFPIA that the European pharmaceutical industry was significantly constrained by the 'lengthy and differing drug registration [approval]

procedures' of the different EU Member States. Moreover, according to the European Commissioner in 1995, the previous 20 years had seen the EU's share of all the world's new medicines developed decline from half to a third, while the US held four times as many patents in the biotechnology sector as the EU. Against this background, Vogel (1998, p. 5) notes:

> An important objective of the creation of a single European drug approval procedure was to promote more European-wide drug research and development, thus helping the industry to confidently continue to hold its place on the world stage in the foreseeable future.

In fact, transnational European harmonization of drug regulation dates back to 1965 in the form of policy statements (or 'directives') from Brussels, which were intended to provide a common framework agreed by the Member States of the EC and (subsequently) the EU. Unlike the FDA's single-minded historical mission to protect public health under the 1938 Food, Drug and Cosmetic Act, together with its 1962 Amendments, the roots of the European pharmaceutical regulation reveal the dual principles of the Commission's perspective – the protection of public health *and* the free movement of products within the EC (European Commission 1965; 1995, p. 35).

Ten years later Directive 75/319/EEC established a European expert body, namely the Committee for Proprietary Medicinal Products (CPMP) 'to facilitate the adoption of a common position by the Member States with regard to decisions on the issuing of marketing authorizations' (European Council 1975). That same directive created the first transnational marketing approval system in the EC based on the expectation that Member States would voluntarily endorse each others initial evaluations – an endorsement known as 'mutual recognition'.

In theory, such transnational mutual recognition could save drug companies and regulators time compared with multiple separate national applications and regulatory reviews. However, this voluntary procedure failed because Member States frequently refused to mutually recognize each others assessments in terms of safety and/or efficacy. Consequently, pharmaceutical companies became and/or remained sceptical about the advantages of using the EC procedures over national regulatory systems. This led to poor uptake by the industry, with most new drug applications between 1975 and 1995 being submitted via national, rather than EC, routes (Cartwright and Matthews 1991).

In 1987, recognition of the increasing technical complexity of some new drugs led to a separate European regulatory procedure mandatory for biotechnology-based drugs and optional for other some new drugs, including NASs. A product was assessed by one Member State (called the 'rapporteur') on behalf of the EU. After all the other Member States and the pharmaceutical manufacturer had commented on the assessment, if the CPMP approved, then marketing authorization was permissible in all Member States. However, *CPMP opinions were not binding on Member States*, so this procedure was not sufficient to achieve a single EU pharamaceutical market (Sauer 1997, p. 3).

Conscious of the limitations of these early voluntary procedures with respect to Europeanization, in the late 1980s, the pharmaceutical industry set out its 'blueprint for Europe'. The industry stressed that any new Europeanized system should enable companies to obtain a single, uniform marketing authorization quickly (within 210 days). While the industry wanted regulators to submit to stringent timeframes and guidelines, it also argued for the maintenance of three approval tracks (national, decentralized, and supranational-centralized) so that firms had maximum flexibility in deciding within which regulatory context to place their drug applications. Specifically, the industry proposed that there should be a centralized EU drug regulatory agency to handle biotechnologically-based drugs, while companies could retain the option of submitting non-biotechnological, innovative pharmaceuticals to either a decentralized EU authority or national regulatory agencies within a mutual recognition procedure. Crucially, the industry recommended that if national regulatory agencies failed to mutually recognize each others assessments within a specified time, then the EU drug regulatory agency could impose a decision on the Member States (Anon. 1988i, p. 7).

As we have seen, by the early 1990s, three key EU Member States with major pharmaceutical sectors (Germany, the UK, and France), together with a fourth important Member State in waiting (Sweden) had governments committed to less state regulation of private industry and sympathetic to further European integration.[9] The shaping of the EU supranational drug regulatory system, which was becoming established during the early and mid 1990s, was strongly influenced by those neo-liberal developments taking place in many of its most important Member States (Abraham and Lewis 2000). Furthermore, within the Commission, pharmaceutical regulation fell under the brief of the Directorate-General (DG) Enterprise, rather than DG Health,[10] until 2010 when it was decided by the President of the European Commission,

Jose Manuel Barroso, to transfer responsibility for EU pharmaceutical policy to DG Health (Anon. 2009a). DG Enterprise was the department responsible for promoting trade and industry, so it was particularly receptive to the concerns of the drug industry. For all of these reasons, combined with the fact that alternative voices from patients, health professionals, consumer organizations, and public health advocacy groups were relatively weak in Europe, a new EU-wide drug regulatory system was established in 1995 largely consistent with the demands of the industry.

On 1 January 1995, the European Medicines Evaluation Agency (EMEA) was created, with headquarters in London, to administer the new systems of EU drug regulation. The CPMP, which changed its name to the Committee for Human Medicinal Products (CHMP) in 2004, remained the key expert EU regulatory body, comprising 30 members – two regulators from each of the 15 Member States at that time. Together the EMEA and the CPMP formed the core of supranational EU pharmaceutical regulation, though formally the European Commission and European Council, both had to ratify the CPMP's opinions into decisions. Simultaneously, the supranational EU 'centralized procedure' was established. It was mandatory for technologically advanced medicinal products, including most biotechnology-derived products, and optional for other innovative pharmaceuticals. Assessment under the centralized procedure was via a single application to the EMEA, and crucially CPMP opinions *became binding on Member States* (European Council 1993; 1996, pp. 31–49). Hence, marketing approval via the centralized procedure provided a company with an immediate, single European licence to sell its pharmaceutical product across the whole of the EU (bypassing entirely national regulatory agencies), just as an FDA approval enabled a firm to market its product across the US.

As the industry had requested, this supranational regulatory agency and system was complemented by a new mutual recognition system and a national route available for non-biotechnological pharmaceutical products that could be innovative or non-innovative. Within the new mutual recognition system, failures between Member States to mutually recognize each others assessments became disputes to be settled at the EU level by CPMP 'arbitration', which was *binding on Member States* (Anon. 2005a). Thus, the decentralized procedure enabled pharmaceutical firms to gain simultaneous marketing approval across part of the EU, say three, four, five or more Member States. As Abraham and Lewis (2000) found, the industry wanted this flexibility in case companies felt that they would have a better chance of marketing some products by

avoiding particular Member State regulatory agencies or the EMEA, or that they lacked the marketing capacities/incentives to launch some products across all parts of the EU.

A drift towards increasing supranational Europeanization has continued since 1995, though by the early 2000s, only 60 per cent of NASs went through the centralized procedure probably because of the high rejection rate recorded in the late 1990s (Anon. 2001a; 2002a). Under Regulation 726/2004, however, from November 2005 it became compulsory for orphan drugs and innovative drugs to treat AIDS, cancer, diabetes, and neurodegenerative diseases, as well as biotechnology-derived pharmaceuticals, to be assessed by EMEA and the supranational centralized procedure, with the expectation that EMEA and the CHMP (the CPMP's successor) within the supranational centralized procedure would continue to expand its reach (Anon. 2005b). In May 2008, innovative drugs to treat viral diseases, autoimmune diseases, and other immune dysfunctions were added to the list fuelling the expectation that EMEA and the centralized procedure would, in time, take over the marketing approval of all innovative pharmaceuticals in the EU (Anon. 2008b). Given our focus on innovative pharmaceuticals in this book, henceforth, our discussion of EU drug regulation will be almost entirely concerned with the supranational level and the centralized procedure, involving the EMEA, CPMP/CHMP, European Commission, European Parliament, and European Council. In 2004, the EMEA changed its name to the European Medicines Agency and adopted the abbreviation, 'EMA' in 2010.

Congress and the conservative 'FDA reform movement' 1995–1997

The election of President Bill Clinton to the White House for two consecutive terms from January 1993 to December 2000 interrupted the New Right's control of the US Administration, but not neo-liberalism. By November 1994 the Republican Party, which provided a home for most of the New Right politicians in the US, for the first time in decades, controlled both houses of Congress. The Republicans had substantial majorities, although not the two-thirds majority needed to override a Presidential veto. Nonetheless, neo-liberal reform of the FDA returned to the political agenda in Washington. Within a few months of the 1994 Congressional election results, Newt Gingrich, speaker of the House of Representatives and leading New-Right politician, announced that he was enlisting the help of conservative Washington-based think-tanks

to work on proposals to 'overhaul' the FDA (Anon. 1994b) Later that year, a former legislative assistant to Senator David Durenberger, told an industry meeting that it would see 'enormous responsiveness' to its frustrations with the FDA amongst the new Congressional majority and suggested that industry had a unique opportunity to lobby for change at the FDA (Anon. 1994c). Industry responded with alacrity to these invitations. By February 1995, the Pharmaceutical Research and Manufacturers' Association (PhRMA) was working on FDA reform proposals (Anon. 1995a).

PhRMA's plans for FDA reform took the form of detailed, draft legislation circulated to key government figures on Capitol Hill. The association's proposals included amendments providing for: (1) a new FDA mission statement emphasizing timely availability of safe and effective products; (2) the establishment of a permanent DHHS panel to evaluate the impact of FDA regulation on the competitiveness of the US drug industry; (3) new NDA requirements allowing submission of more safety and efficacy data as summary tables; (4) following the French system, the use of contract reviewers, external to the FDA (known as third-party review), whenever agreed by the pharmaceutical company; (5) a new drug approval standard that could consist of data from only one well-controlled clinical trial instead of the two, which had been required since the 1962 Drug Efficacy Amendments to the 1938 Food, Drug and Cosmetic Act; (6) a presumption of approval for drugs already approved by the EMEA or the UK MCA, so that the FDA would have to decide on NDAs within six months, based on the original submission without being able to request any further data and rejection would only be allowed if the drug had been demonstrated to be unsafe or ineffective (Anon. 1995b).

Some New-Right think-tanks also published proposals. One, Newt Gingrich's Progress and Freedom Foundation, drafted recommendations to privatize the drug regulatory review process by using contract reviewers outside the FDA (Anon. 1995c; 1996a). The pharmaceutical industry, however, was less enthusiastic about plans for wholesale privatization of the drug review process because they were concerned that such a move would undermine consumer confidence in prescription drugs. Commenting on the proposals of Gingrich's Foundation, PhRMA stated its preference that the FDA should retain responsibility for NDA reviews, assisted by occasional third-party review when felt necessary. The PhRMA sought reduction of regulation in ways likely to maximize industry interests, rather than ideologically-driven privatization (Anon. 1995c). Congress's first draft bills in summer 1995 largely reflected the

proposals put forward by PhRMA. One of the bills even repeated verbatim the language of PhRMA's draft legislation (Anon. 1995d; 1995e; 1995f; 1995g). A consumer advocate during negotiations about this legislation claimed to have seen a draft of the bill, parts of which were left blank with the words: 'Industry inserts language here'.[5] Whether or not that is correct, it is clear that New-Right reformers in Congress were highly influenced by industry preferences and moderated their legislative proposals at the behest of PhRMA.

The New-Right foundations, especially the Washington Legal Foundation, paid for a series of anti-FDA advertising throughout 1995 and 1996 accusing the agency of killing Americans with over-cautious drug regulation. PhRMA arranged to fly in 140 patients to Washington to talk with the legislators about how the FDA had deprived them of life-saving drugs. However when PhRMA provided the *Washington Post* with the names of some of those people for the *Post* to contact, the newspaper reports did not include one story where a patient's problems could have been addressed by the proposed FDA reforms. Indeed, according to Hilts (2003, pp. 309–11), their problems were not even within the control of the FDA.

The New-Right's campaign for FDA reform had political clout in the mid-1990s, but little evidence to support it. By 1994, FDA drug review times had declined dramatically and were as fast as those of the UK's MCA, and faster than those in France, Spain, Germany, Australia, Japan, Italy and Canada (FDA 1997c; Hilts 2003, pp. 316–18). Furthermore, the agency was the first regulatory authority in the world to approve five out of the six available AIDS therapies and a number of drugs considered to be 'breakthroughs', such as Taxol, Fludarabine, Pulmozyme, Riluzole, Cognex and Betaseron. By the mid-1990s, the 'drug lag thesis' still peddled by the Washington Legal Foundation and the editorial page of the *Wall Street Journal,* was little more than ideologically driven fantasy (Anon. 1995h; Hilts 2003, pp. 297–303).

Aware of this, some patient groups became alarmed at the Congressional reform proposals and increasingly annoyed that none of the organized interests pressing for reform had bothered to ask the patient groups what they thought. [8] Consequently a number of patient advocacy groups collaborated to form the Patients' Coalition in 1995.[11] By 1997, it comprised over 100 organizations representing patients with serious, rare and life-threatening disorders (Patients' Coalition 1997). This was the largest mobilization of patient groups in the US since AIDS activism, and arguably more significant because it crossed a large number of disease categories. The Patients' Coalition argued against

many of the proposals for FDA reform put forward by both the House and the Senate, such as statutory review deadlines which, if exceeded, could trigger either a 'European hammer' whereby drugs approved by the EMEA or MCA would automatically be approved in the US. The Patients' Coalition also opposed the suggestion that NDA approval should be based on a single clinical trial, though the Coalition was willing to support a 'single-clinical-trial' rule in exceptional circumstances where the single study was very persuasive in demonstrating a direct therapeutic benefit on a clinical endpoint (Anon. 1996b; 1996c; Patients' Coalition 1996).

According to the Coalition, patient groups speaking in favour of the reform proposals were either 'astroturf' organizations or relied on industry for funding.[5,7,8] Moreover, as part of their campaign, the Patients' Coalition commissioned an opinion poll, which indicated that only 22 per cent of those polled believed that the FDA was a 'big government bureaucracy' (Patients' Coalition 1997, p. 2). This was despite a barrage of prominent newspaper and television advertisements and 'info-mercials', paid for by industry and the right-wing foundations, claiming that FDA regulation was responsible for the deaths of thousands of American patients (Hilts 2003).

Thus, there is little evidence from the mid-1990s that patients groups or the general public were pushing for further acceleration of the drug review process or further lowering of regulatory standards in the way that the AIDS activists had done in the late 1980s. On the contrary, many of the early AIDS patient advocates from the 1980s played key roles in *opposing* the Congressional reform proposals in 1996 precisely because of what they had learnt from their close involvement with the regulatory science of AIDS treatment. In particular, all of the American AIDS patient groups began to stress the importance of trials that generated knowledge concerning the optimal use of the available drugs (Epstein 1997).

Analysis of documents from the most active AIDS patient groups reveals that they opposed further lowering of regulatory standards despite claims by the proponents of the reforms that the new legislation would 'facilitate the timely availability of new products' (US Senate 1996). In urging rejection, AIDS patient advocates noted that the US had fewer drugs withdrawn for safety reasons than other countries (Link 1995). Evidently, *safety,* not merely speed of approval, was of primary importance even for these patients with life-threatening conditions. Significantly, the AIDS patient advocates argued against many of the proposals that were ostensibly designed to quicken patient access,

for instance: third party reviews, shortening the time FDA had to review critical safety data before allowing trials in humans to go ahead, and the introduction of rigid new drug review timeframes (AIDS Action Council 1996).

Many of the New Right reform proposals of 1996 were also opposed by the FDA and the Clinton Administration, which held the power of presidential veto over Congressional proposals (Anon. 1996b). In 1996, the drug industry urged Republicans in Congress to drop some of the more 'extreme' deregulatory proposals of 1995 in order to secure greater bipartisan support in Congress, so that a Presidential veto by Clinton's Democratic Administration could be avoided and the legislation could be passed quickly (Anon. 1996d; 1996e). Towards the end of that year, industry and the FDA began negotiations on the reauthorization of PDUFA I, due to expire in 1997. PhRMA's plan was to secure the agency's agreement on a number of FDA reforms as conditions of such reauthorization. PhRMA and the FDA agreed that the controversial proposal on mandatory third-party (privatized) reviews should be discarded. However, the industry now sought timeframes for meetings with FDA management as well as for drug review; the PDUFA I drug review timeframes to be further reduced; and continued to press for only one pivotal clinical trial to be required to demonstrate efficacy for all new drugs (Anon. 1996f). By February 1997, the FDA agreed to most of these conditions (Anon. 1997a; 1997b).

The industry managed to secure concessions from the FDA on off-label promotion, even though the Patients Coalition asserted vigorously that off-label promotion was a hazard to the American public and presented a direct threat to the nation's health (Anon. 1997c; Patients Coalition 1997, p. 5). By contrast, with respect to accelerated approvals, a provision supported by consumer and patient advocacy groups, which would have imposed fines on pharmaceutical firms that failed to conduct confirmatory post-marketing studies, was watered down to requirements on companies to submit progress reports on such studies each year until completion (Anon. 1997c; 1997d). The House and Senate bills were reconciled on the 8 November 1997 and passed by Congress as the Food and Drug Administration Modernization Act (Anon. 1997e). Despite all their campaigning efforts, and in sharp contrast to the pharmaceuticals industry's influence on the Food and Drug Administration Modernization Act (FDAMA), proposals from patient groups that significantly conflicted with industry's interests were not adopted into FDAMA.[8]

FDAMA and fast-track drug development and review

As we have seen, like PDUFA, and unlike the 'Subpart E' and 'Subpart H' rules, FDAMA was mainly about general FDA reforms affecting all types of drug product regulation. However, within that, it codified the 1992 Accelerated Approval (Subpart H) rule into the statute. Relatedly, section 112 of FDAMA added a new section to the 1938 Food, Drug and Cosmetic Act. The new section 506 allowed companies to seek 'fast-track' designation for their product development programmes concurrently with, or at any time after, submission of an IND application. Largely reiterating the criteria for eligibility under the 1992 Accelerated Approval rule, a drug could qualify for fast-track designation, if it was intended for the treatment of a 'serious' or life-threatening condition *and* its development programme evaluated the product's potential to address 'unmet medical needs' for such a condition. The programme became referred to as 'a fast track drug development program' (FDA 1998a, p. 3). A 'serious' condition was defined as one impacting on survival or associated with morbidity substantially affecting day-to-day functioning 'but the morbidity need not be irreversible, providing it is persistent or recurrent' (Federal Register 1992; FDA 1998a, p. 4). Thus rheumatoid arthritis or depression could meet the definition of 'serious' for the purpose of fast-track designation. An 'unmet medical need' was defined as a medical need not addressed adequately by existing therapies, including products that demonstrate potential advantages over existing alternative therapies in terms of improved effects on serious outcomes or avoidance of serious toxicity (FDA 1998a).

The FDAMA specified some ways in which product development and review could be expedited. For instance, it permitted 'rolling' NDA submission and FDA review of discrete portions of a new drug application before the company submitted a complete application. FDAMA stipulated that manufacturers of fast-track products had a right to request meetings at various stages of the drug's development. Following this legislation, FDA's guidance to industry stated that 'appropriately timed meetings between the regulated industry and FDA are a critical aspect of efficient drug development ... to ensure that the evidence necessary to support marketing approval will be developed and presented in a format conducive to an efficient review' (FDA 1998a, p. 10). For drugs with fast-track designation, meetings between the manufacturer and the agency to discuss product labelling issues were to be scheduled early in the review process.

Following the neo-liberal trend: funding and review times in the EU

By the time EMEA was created in 1995, many countries had taken the neo-liberal route of funding their drug regulatory agencies via industry fees. In Europe, this varied from 50 per cent funding in Germany to 100 per cent in the UK, while under PDUFA I, industry fees made up 36 per cent of the FDA's spending on new drug review in 1995, rising to 62 per cent in 2010 (see Figure 2.1). From its inception, supranational EU drug regulation accepted the principle that the EMEA should be partly funded by fees from pharmaceutical firms reflecting the dominant neo-liberal perspective within the Member States of the EU.

Like the European Member States, fees collected from drug companies for regulatory work by the EMEA contributed to the overall revenues of

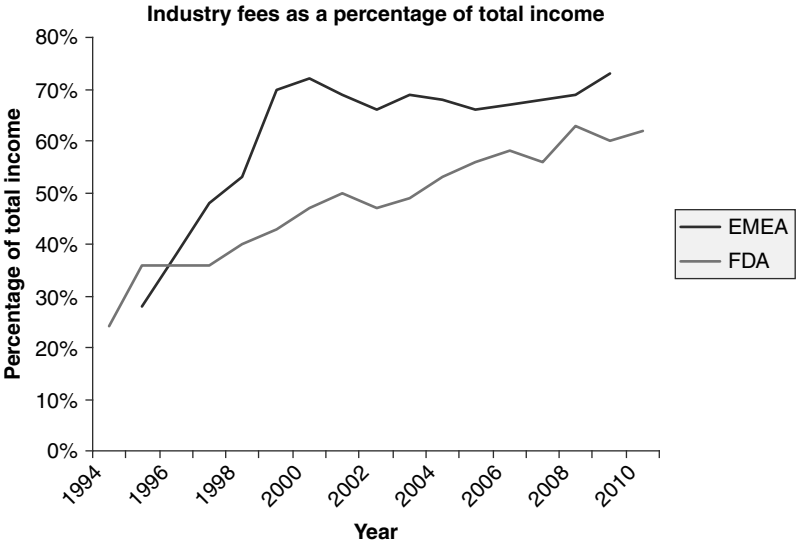

Figure 2.1 Percentage of industry fee contribution to total EMEA budget and to FDA spending on new drug review

Figures for FDA for 1994–1999 were compiled from 65 Federal Register 47994 and for 2000–2010 were compiled from Annual Financial Reports to Congress, available at: http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/FinancialReports/PDUFA/default.htm (Accessed 15 October 2011).

Sources: Figures for EMEA for 1995–2000 were compiled from EMEA Annual Reports. Figures for 2000–2009 taken from Ernst & Young 'European Commission Evaluation of the European Medicines Agency – Final Report – January 2010'. Available at: http://ec.europa.eu/health/files/pharmacos/news/emea_final_report_vfrev2.pdf (Accessed 15 October 2011).

the agency. Unlike the FDA, the EMEA was not restricted to using fees collected solely for new drug review or other specific purposes. In its first year, the EMEA collected industry fees to the tune of just 28 per cent of its total annual review. Thereafter, however, it pursued industry fees vigorously, quickly overtaking the FDA in this respect, and reaching over 70 per cent funding from companies in the late 2000s. As shown in Figure 2.1, the proportion of funding contributed by industry towards total EMEA revenues and towards FDA spending on new drug review has increased over the years. In 2002, a group of CPMP members unofficially published an open letter stating that the independence of the EMEA should be strengthened by reducing the proportion of its budget financed by industry fees, but that argument fell on deaf ears, as the agency's financial dependence on industry fees subsequently increased (Anon. 2002b).

According to Sauer (1997, p. 2), the first executive director of the EMEA, the centralized procedure was intended to operate as a 'fast track' system for obtaining a marketing authorization in Europe. It was expected to have a major impact on shortening new drug review times (Thomas *et al*. 1998, p. 788). Accordingly, in line with demands from industry and managers of national drug regulatory agencies in Europe who subscribed to the neo-liberal regulatory state, the supranational centralized procedure was established with strict and fairly rapid timeframes. The total amount of time allowed for the CPMP to arrive at its opinion was set at 210 days (European Commission 1996, p. 43). However, unlike the FDA's system, which differentiated between innovative pharmaceuticals receiving priority review (due to their promise of modest or significant therapeutic advance) and drug innovations receiving standard review (offering little or no therapeutic advance), the EMEA introduced no formal mechanisms for distinguishing between products that were innovative in a merely technical sense and those that promised therapeutic advance.

Nevertheless, the EMEA operated an *informal* accelerated evaluation arrangement for products intended to treat heavily disabling or life-threatening diseases, where there was an absence of appropriate alternative therapies, and where there was anticipation of 'exceptional high therapeutic benefit'. In such cases a final CPMP opinion could be adopted within 120 days, but that was at the discretion of the CPMP and EMEA (CPMP 1996). That arrangement was much more restrictive than the FDA system granting priority review status, which was open to life-style pharmaceuticals and drugs to treat less serious diseases with no requirement that expected clinical benefit must be very high. Whereas

the FDA's priority (or standard) review 'track' allocation was routine practice for all innovative pharmaceuticals in the US, according to both European regulators and industry, the informal 120-day track in the EU centralized procedure was intended to be, and was, used only rarely (CMS Cameron McKenna and Andersen Consulting 2000, p. 174). In 2004, this accelerated assessment procedure was formalized in legislation by the European Parliament with a new time-frame of 150 days (Anon. 2005c; 2006a).

Table 2.2 shows that every year (1995–2010) the EU timelines were adhered to, with 13 out of these 16 years showing an assessment time of less than 190 days (range 157–203 days), compared to a target time of 210 days. Following the FDA's consultative approach to industry, the EMEA explicitly advised companies planning to submit NDAs through the centralized procedure to meet with EMEA staff beforehand for regulatory advice to help ensure quicker validation of applications (Anon. 1998a). Those suggestions may have been a response to the growth in EU non-approvals in the centralized procedure from 11 per cent in 1995 to 41 per cent in 1998. Subsequently, the rejection rate fell to 23 per cent in 1999, 21 per cent in 2000 and 27 per cent in 2001 (Anon. 2002c).

Table 2.2 EMEA approval times for centralized procedure products 1995–2010*

Calendar year	EMEA assessment phase (days)	EMEA post-opinion phase (days)	Decision process (days)	Total (days)	Total (months)
1995	189	45	119	353	11.6
1996	169	40	79	288	9.5
1997	178	32	86	296	9.7
1998	185	42	83	310	10.2
1999	183	38	70	291	9.6
2000	178	45	71	294	9.7
2001	170	32	76	278	9.1
2002	192	31	61	284	9.3
2003	190	48	60	298	9.8
2004	187	7	94	288	9.5
2005	203	56	41	300	9.9
2006	171	36	31	238	7.8
2007	171	25	33	229	7.5
2008	184	24	45	253	8.3
2009	157	29	42	228	7.5
2010	167	20	59	246	8.1

**Sources*: compiled from data on review times contained in EMEA Annual Reports.

Europe's innovation quest and the legislative review: from 'exceptional circumstances' to 'conditional marketing'

Article 71 of Regulation 2309/93 required the European Commission to report on the progress of the EU's supranational drug regulatory system within six years of the EMEA's creation. Consequently, in 2001, the Commission initiated a sweeping review of EU pharmaceutical legislation, which culminated in 2004 in a new Regulation (Regulation 726/2004) and a new Directive (Directive 2004/27/EC) amending Directive 2001/83/EC. This major review of EU pharmaceutical regulation confirmed concerns that the European pharmaceutical industry was losing competitive ground to the US in terms of research activity and product innovation (Gambardella *et al*. 2000, pp. 83–4). As we shall see, this broader context, and the fact that DG Enterprise was tasked with promoting the competitiveness of the European pharmaceutical industry, largely framed the responses and activities of the Commission throughout the review.

While any new legislative proposals arising out the review would, ultimately, have to be approved by the European Parliament and the European Council, the role of the Commission was particularly significant since it is the Commission alone of all the EC institutions that has the power to propose and draft new legislation. In theory, Commission proposals are meant to be consistent with the broad directions laid down by the Council. However, the Commission's initial draft proposals for new pharmaceutical legislation ignored specific Council recommendations where these were seen as being inconsistent with industry interests. For example, at the 2281st Council meeting of Health Ministers in June 2000, the Council invited the Commission, as part of the 2001 legislative review, to address the Council's resolution that 'identification of medicines with significant added therapeutic value is of great importance to promote innovation, which is vital not only from a health-protection perspective but also from an industrial policy viewpoint' (Europa, 2000). The Commission appeared to disagree, commenting that regulation was not the appropriate way of achieving this aim (La Revue Prescrire, 2002, p. 11) and neither the new Directive nor the new Regulation included comparative clinical data requirements that would allow the EMEA to differentiate between medicines on the basis of whether or not they offered added therapeutic value.

In contrast, the Commission was quick to include proposals that promoted industry interests, such as accelerated regulation of innovative pharmaceuticals within the centralized procedure (Bardelay and

Kopp, 2002; European Commission 2001a, p. 14). The Commission proposed two solutions: first, the formalization in legislation of an accelerated assessment process; and second, a provision which would permit the 'conditional' authorization of innovative drugs within the centralized procedure. This conditional marketing approval would allow for the early marketing of new drugs based on less trial data than normal (European Commission 2001b, p.4). As we have seen, in 1988 and 1992, the FDA introduced regulations (the accelerated approval regulations) pertaining to drugs intended to treat serious, debilitating or life-threatening conditions, which permitted the agency to approve drugs on to the market on the basis of less evidence of safety and efficacy – including reliance on phase II instead of the regular phase III trials and non-established surrogate endpoints. Since 1993, Article 13(2) of Regulation 2309/93 has allowed the EMEA to approve new drugs on to the market that lack comprehensive data on quality, safety and efficacy in 'exceptional circumstances' (European Council 1993). However, this provision was quite different from the FDA's accelerated approval rule in the sense that it was intended to be used only in cases where collection of full efficacy and safety data was judged to be impossible on ethical or scientific grounds (European Council 1975, Annex, Part 4 G).

When first introduced in the 1990s, the EU's 'exceptional circumstances' provision was well-received, particularly by groups representing patients with rare diseases because there can be genuine difficulties in obtaining adequate safety and efficacy data in the context of very small patient populations (CMS Cameron McKenna and Andersen Consulting, 2000: 45). In fact, figures on the number of products approved under the EU's exceptional circumstances regulation suggest that, in practice, it was being used more broadly than the restrictive criteria implied (Garattini and Bertele, 2001, p. 66). According to the EMEA, in the ten-year period before 2006, approximately 18 per cent of all products approved by the European agency were approved under exceptional circumstances (EMEA 2000, p. 7; FDA 2011b, p. 252).

Some former EU regulators told us that pharmaceutical firms were designing drug development programmes aimed at meeting the requirements for accelerated approval under Subparts E and H in the US and then submitting the results of those studies to the EMEA for approval under the exceptional circumstances provision. The EMEA and CPMP were then under pressure to adapt the EU's exceptional circumstances provision to companies' imperative for access to the US market. One former member of the EU's CHMP suggested that representations of

patients' needs also sometimes influenced the way in which EU regulators applied the exceptional circumstances provision:

> After all, there are emotional aspects involved. And when you say: 'this is an unmet medical need, we must do something for these patients, there is nothing at this moment'. It is an argument that many people are taken in by. I don't buy that because I believe that if there is an unmet need, you need to make sure that you *meet* the need, not that you establish another way of continuing the unmet need by showing that hypothetically you have solved the problem even if you have done nothing [interviewee's emphasis].[12]

Yet despite the fact that EU regulators were clearly prepared to go beyond the limits imposed by the exceptional circumstances provision, in 2004 the new pharmaceuticals legislation included a requirement that the Commission draft regulations that would allow for conditional marketing approval. As mentioned above, the legislation also required that the EMEA establish an accelerated assessment procedure which, like the FDA's priority review, would guarantee quicker assessment times of companies' marketing applications. Specifically, the preamble to Regulation (EC) No 726/2004 stated:

> In order to meet, in particular, the legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies, accelerated assessment procedures should be set up, reserved for medicinal products of major therapeutic interest, and procedures for obtaining temporary authorization subject to certain annually reviewable conditions. (European Parliament and Council 2004, para 33)

While the official justification for introducing new mechanisms to accelerate review and grant early drug approval was the 'legitimate expectations of patients', the evidence suggests that the main impetus for more accelerated approval mechanisms in Europe came from the pharmaceutical industry and from within the Commission itself.

In a consulting report for the Commission, CMS Cameron McKenna and Andersen Consulting (2000) documented that the industry was pressing for an extension of the exceptional circumstances provision to cover products intended to treat serious or life-threatening conditions where no effective therapies were available, *and* a formal accelerated evaluation procedure for medicinal products offering a significant

benefit over current therapies. Evidently, the industry was advocating for regulations in the EU that mirrored the accelerated approval and priority review procedures in the US. In their survey of pharmaceutical firms marketing drugs in the EU, Cameron McKenna and Andersen found that 63 per cent agreed or strongly agreed that the exceptional circumstances procedures should be more widely available, and 94 percent agreed or strongly agreed that a formal procedure for fast-tracking drugs should be established (CMS Cameron McKenna and Andersen Consulting 2000, pp. 172–6).

Industry was dissatisfied with the exceptional circumstances provision because companies believed it was too restrictive in scope and used too infrequently. Notably, the European Biopharmaceuticals Enterprises (EBE), a group within EFPIA representing biopharmaceutical companies, contended:

> The regulatory evaluation of certain innovative medicinal products to fulfil urgent, unmet, medical needs – and, consequently, patients' access to such therapies in Europe – is unnecessarily lengthy. We believe this is partly due to the absence of a coherent series of mechanisms in the European Union to permit accelerated market access for innovative and much needed new medicines. (EBE-EFPIA 2004, p. 1)

Such sentiments were echoed by the EU Commissioner for Enterprise, who claimed that the EU system needed to take account of the 'new global environment' by adopting conditional marketing approval to ensure that regulatory assessment of major new drugs could be 'as fast, if not faster than the FDA' (quoted in Anon. 2001b). Notably, this pronouncement also echoed arguments made by the G10 Medicines Group – a collaboration of European industrialists, Health Ministers, and patient groups, created by the European Commission to advise it on EU policy for the pharmaceutical industry (Anon. 2002d).

By contrast, a significant majority, 70 per cent, of European regulators (outside the European Commission), who were interviewed by Cameron McKenna and Andersen *opposed* making the exceptional circumstances provision more widely available. Our interviews with European regulators on this point revealed that they wanted to use, and did use, the exceptional circumstances provision for cancer drugs and drugs for serious diseases where there was little or no available treatment.[13] However, they were concerned that drug companies would abuse (post-marketing) follow-up commitments to provide more comprehensive evidence of therapeutic benefit, which also explains why these regulators

were found to support stronger powers to withdraw marketing approval after one year if companies failed to comply with their post-marketing commitments (CMS Cameron McKenna and Andersen Consulting, 2000, pp. 173–4). Indeed, in 1999, some EU regulators had warned that a 'large number' of companies were failing to meet their post-marketing commitments, including safety and efficacy studies (Anon. 1999a).

Similarly, 87 per cent of European regulators surveyed were opposed to introduction of a formal fast-track procedure (like the 'priority review' system at the FDA) on the grounds that the existing systems at that time were sufficiently flexible for regulators to prioritize and accelerate new drug applications which were likely to have important public health benefits (CMS Cameron McKenna and Andersen Consulting 2000, pp. 45 and 175). As one former member of the CHMP explained, an application with sound evidence supporting the breakthrough status of a drug can be approved very quickly without special procedures.[12]

Of the patient representatives consulted in the same survey, only 49 percent supported the extension of the exceptional circumstances provision (CMS Cameron McKenna and Andersen Consulting 2000, pp. 174–6). It is unclear how many of the patient groups that responded were funded by pharmaceutical companies, and if so, to what degree. According to the consulting firm, 'national consumers organizations, together with 134 associations representing a broad spectrum of disease areas and countries were sent written questionnaires', of which 31 associations responded (CMS Cameron McKenna and Andersen Consulting 2000, pp. 25–6). There is, however, no evidence that patient associations or public health advocacy groups initially sought or demanded these changes to the exceptional circumstances provision (Anon. 2002e).

Notably, when we interviewed Commission officials, demand from patients did not feature at all in their explanations of the emergence of 'widening exceptionality'. On their account, the reasons behind the proposals related to: harmonization of European and US regulation, which the Commission saw as 'exceptionally important – both for stimulating innovation, for reducing burdens on industry, and for improving public health protection'; addressing industry demands; and levering companies to complete post-marketing studies.[14] The point about levering companies to complete post-marketing studies refers to the fact that, before 2004, the EMEA's only regulatory option if a pharmaceutical firm failed to comply with its post approval obligations made to the agency at the time of marketing approval (e.g. the completion of some post-marketing drug trial) was to remove the drug product from the market – a measure that regulators were reluctant to take when

the drug benefited some patients. With the introduction of conditional marketing regulations in 2004, the EMEA was empowered to impose financial penalties on non-compliant companies, but such enforcement capabilities could have been achieved separately without conditional marketing (European Commission 2002; European Parliament and Council 2004).

While there is no evidence that EU patients were demanding earlier or faster access to innovative pharmaceuticals in the EU, there *is* evidence that some patient and consumer health advocacy groups were concerned that the draft proposals released by the Commission in 2001 prioritized industry interests over the interests of EU citizens and public health (La Revue Prescrire, 2004). In March 2002, a lobby formed in Paris – comprised of patient groups, family and consumer advocacy organizations, health insurance associations and health professional bodies – whose purpose was to 'ensure that European pharmaceutical policy serves the public interest' (European Public Health Alliance, 2003). And between 2002 and 2004, this coalition – the Medicines in Europe Forum (MiEF) – was the most visible and active civil society group lobbying the EU Parliament, Council and Commission for changes to the draft legislation during the period of the legislative review. Significantly, with respect to Commission proposals to accelerate the assessment process, the MiEF fought to *safeguard* the amount of time rapporteurs had (at least 80 days) to analyse the scientific data contained in companies' marketing approval applications. The coalition also fought for, and secured: increased transparency of both the decentralized and centralized procedures; a continued ban on direct-to-consumer advertising; and better labelling and patient information leaflets. In relation to the needs of patients with no effective treatment options, the coalition pressed, not for earlier *marketing*, but for patient access prior to marketing via compassionate use programmes (La Revue Prescrire, 2004).

Despite the absence of pressure from patient and consumer advocacy groups within the EU for earlier marketing of innovative medicines, in November 2004 the Commission published a draft regulation on conditional marketing approval, which was formally implemented as Regulation 507/2006 in April 2006 (Anon. 2006c). Under the regulation, pharmaceutical firms could request conditional marketing approval for new drugs to treat emergencies, chronically/seriously debilitating conditions or life-threatening disease. Companies could also request conditional marketing in the EU for orphan drugs. Conditional approval could be granted by the EMEA if: the drug was of public health interest;

a positive benefit–risk ratio could be demonstrated based on scientific evidence and pending completion of further studies; safety data were complete unless under very exceptional circumstances; and the company was required to finalize on-going studies or conduct new studies to verify the presumed positive benefit–risk ratio.

The purpose of the 'conditional marketing' regulation was to permit pharmaceutical companies to get innovative drugs in these categories approved on to the market faster with less clinical (and possibly less preclinical) test data than normally required for regular approval. 'Conditional marketing' was granted only if (or on the condition that) the company committed to undertake post-marketing studies to provide additional datasets that would answer any outstanding questions and data-deficiencies about the safety and efficacy of the drug in question. In this respect, the EU's 'conditional marketing' regulation was very similar to the FDA's 1992 'accelerated approval' rule in the US. Conditional marketing status in the EU was to be reviewed every year by the EMEA to assess whether any new data provided were sufficient to justify conversion from conditional to regular approval (Anon. 2006c).

Conditional marketing approval met with a mixed response from patient groups and public health advocates. The European patients' organization for rare diseases, EURODIS asserted that it was particularly important for rare diseases, but expressed concern for a more 'flexible' approach should a company fail to fulfil post-marketing conditions in time for annual renewal:

> Not renewed means that the product is withdrawn from the market. When the product is in fact useful, but only the incompetence or negligence by the applicant [company] are in question, then maybe the price [meaning loss to health] to pay for the applicant to be incompetent is too high for the patients. When the applicant does not respect the condition because for example lack of financial resources to conduct appropriate studies, it is a problem to withdraw from the market a potentially useful product that maybe has a positive benefit-risk ratio. (EURODIS 2005)

By contrast, the MiEF argued that the approval criteria were too vague and the (post-marketing) follow-up requirements too flimsy. According to the MiEF, conditional marketing could be justified only in very exceptional circumstances of urgent public health need because, by allowing inadequately assessed products to enter the European market, the procedure was inherently risky (MiEF 2004).

Probably due to the creation of the 'conditional marketing' regulation, in 2007 the European Commission introduced financial penalties for drug firms that failed to meet their post-marketing commitments for products approved through the centralized procedure. It is remarkable that 12 years elapsed before companies faced significant penalties for neglecting post-marketing obligations to regulators and public health. Initially, the Commission proposed that the fine should be ten per cent of the offending company's turnover in the previous year, but that was reduced to five per cent after the pharmaceutical industry protested that ten per cent was too punitive (Anon. 2007a).

Even after the introduction of 'conditional marketing approval' and 'accelerated review' within the EU's supranational centralized procedure, the pharmaceutical industry and the European Commission's DG Enterprise continued to press for faster marketing approval of innovative drugs. A report by a group of experts advising the Commission on how to improve the EU's performance in research and innovation asserted that, in 1992, six of the top ten selling pharmaceuticals were produced by European firms, but by 2002 this had fallen to just two of the top ten. That situation apparently prompted the inference that the Commission should do even more to accelerate patients' access to innovative drugs (Anon. 2006d). Yet the *sales* of pharmaceuticals are not necessarily an indication of innovation, let alone therapeutic advance or patient need.

In June 2005, the EMEA set up a think-tank comprising EMEA staff and the agency's scientific bodies. Aware of the declining number of pharmaceutical product innovations in the EU, the think-tank sought to identify 'bottlenecks' in the development of innovative drugs. It met with drug companies and sent 200 firms a questionnaire. In response to industry concerns, two billion euros were made available to boost drug innovation in Europe via the Innovative Medicines Initiative (IMI), a pan-European public-private collaboration involving pharmaceutical companies, regulatory authorities, patient organizations, universities and hospitals (Anon. 2006e; 2008d). Although a public-private collaboration, with one billion euros coming from EFPIA and the other billion from the European Commission, the IMI was an industry initiative. Following the priorities identified by drug companies, it was particularly focused on reducing the time and cost of drug development, especially by searching for biomarkers and surrogate endpoints that could predict clinical efficacy and minimize the failure (or so-called attrition) rate of late-stage, expensive clinical trials (Anon. 2007b). In this respect, the IMI was similar to the Lasagna Committee

in the US nearly 20 years earlier, though the overall brief of the IMI was broader.

In fact, in 2006, the FDA had established a similar project, known as the Critical Path Initiative (CPI) focusing on biomarkers of drug efficacy and toxicity, whose importance to the FDA was reiterated by its commissioner at the end of the decade (Anon. 2008e; 2010b). The 'conditional marketing approval' regulation in the EU opened the door for industry to seek more extensive use of biomarkers and surrogate endpoints just as the 1992 'accelerated approval' rule had done in the US. The application of biomarkers and surrogate endpoints to drive regulatory approval decisions was much more amenable to industry and regulators in a context of early conditional marketing approval based on incomplete clinical data. The IMI was launched in 2008. Industry spokespeople, such as the director of the ABPI, were quick to represent it as 'an initiative that will bring medicines to patients more quickly and effectively' (quoted in Anon. 2008d, p. 23).

The 'Global Dossier': international harmonization of regulatory science in the EU and US

As we discussed in relation to European harmonization, according to the industry, inconsistencies between national regulatory standards produced wasteful duplication in drug testing, which drove development costs and created barriers to trade. That concern applied not only to national systems within Europe before 1995, but also more internationally (Abraham and Reed 2001).

Reflecting with the neo-liberal outlook of the Reagan Administration, in the mid-to-late 1980s, American-led bilateral initiatives between the US and Japanese governments were taken, including a determined objective on the part of the US to open up Japanese markets (Ferris 1992, 197–8). Japan represented about 20 per cent of the world pharmaceutical market at that time (Reed-Maurer 1994, 38). In response, in 1988, the first 'mission' of government regulators and industry representatives from the pharmaceutical sector in Europe was sent to Japan to discuss bilateral harmonization of regulation between Japan and the EU, so that Japanese markets might become more accessible to the European drug industry (Wyatt-Walter 1995). However, given the importance of the US market (about half the world market), the European pharmaceutical industry was unenthusiastic about solely bilateral harmonization with Japan, so the International Federation of Pharmaceutical Manufacturers Association (IFPMA) took responsibility for organizing

trilateral meetings between the industry and government regulators in the pharmaceutical sectors of the EU, Japan, and the US from 1990 (Abraham and Reed 2001). These meetings became established as the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

During the 1990s, the ICH focused on harmonizing the techno-regulatory standards for new drug approval across the three regions. The idea was that pharmaceutical firms would be able to submit the same pre-clinical toxicological, clinical trial, and post-marketing data in order to meet the regulatory requirements of the three regions – a single dossier of data instead of three (Abraham and Reed 2001).

As with advocates of accelerated regulatory review, proponents of ICH declared that, in addition to expanding industry's access to markets more quickly, it was also in the interests of patients and public health. At the opening session of the first ICH conference in Belgium in 1991, it was asserted that the savings made by companies from harmonized regulations would further the delivery of innovative research yielding therapeutic benefits to patients (Bangemann 1992, p. 4). By the end of the decade, even more emphatic claims were made by IFPMA, which had become the ICH's secretariat:

> ICH clearly enhances the competitive position of those companies that choose to operate using its standards, as well as significantly benefiting both the regulators and the patients, who, most importantly, receive crucial new treatments sooner. …. In summary, harmonization through ICH brings important, life-saving treatments to patients faster, while releasing the pharmaceutical companies' development funds to projects that will produce the ground-breaking treatments of the future. (IFPMA 2000, p. 1)

By 2000, the ICH had indeed harmonized the techno-regulatory standards for safety and efficacy evaluation, as well as other types of new drug assessment, across the three regions. Certainly it was in the commercial interests of pharmaceutical firms because it cut their costs and improved their access to markets for whatever products they developed. In the context of budgetary pressures and relentless demands for more rapid regulatory review, it is easy to see why streamlining of technical data submissions could be attractive to regulatory agencies if it did not undermine their credibility as protectors of public health. Supporters of ICH from industry and regulatory agencies insisted that it did not compromise drug safety. However, independent research has shown

that, in many areas of safety evaluation, harmonization actually entailed a lowering or loosening of protective standards for some countries, often the US (Abraham and Reed 2001; 2002; 2003). Whatever, the drawbacks of ICH for drug safety standards, it was yet another neo-liberal inspired process of reform supposedly to increase the number of innovative pharmaceuticals delivering therapeutic advance for patients faster, by cutting development costs and time.

Pharmaceutical outcomes and the neo-liberal reforms

Evidently, since the 1980s, the FDA and the EMEA have developed mechanisms for accelerating both regulatory review and development of innovative pharmaceuticals, including reductions in the amount of information regulators require from companies before clinical trials and/or marketing approval, and time management goals regarding formal meetings between regulators and firms encouraging regulators to provide companies with scientific advice about drug development. As we have seen those measures within the neo-liberal reform programme delivered much faster new drug review times in the EU and the US than previously. In 1994, the FDA's goal was to finish 55 per cent of its new drug reviews on time; it achieved 95 per cent. In 1995, the goal was 70 percent, but the FDA achieved 98 per cent. The goal rose again to 80 per cent in 1996 when the FDA achieved 100 per cent. In both 1997 and 1998, the goal was 90 per cent and the FDA achieved 100 per cent (Willman 2000a). To reinforce this point, FDA Commissioner Mark McClellan claimed in the agency's 2003 performance report to Congress that 'over the eleven years of PDUFA, the agency had met or exceeded nearly all of the PDUFA goals' (FDA 2003a).

There is also evidence that these measures, perhaps combined with ICH activities, had an impact on accelerating drug development. An analysis of new drug development times between 1990 and 1999 by the Tufts Center found a marked downward trend in average clinical development times in the US. For example, the mean clinical development time for priority drugs was 48 per cent lower in 1998–1999 when compared with 1990–1991, even though the previous three decades had seen steady increases in drug development times (Kaitin and DiMasi 2000). In a subsequent study, the Tufts Center reported that the fast-track designations (such as Subparts E and H) had had the intended effect of shortening drug development times – between 1998 and 2003 the average time required to develop a fast-track drug and gain approval fell by over two years. Moreover, the number of diseases attracting

fast-track designation had expanded (Tufts Center for the Study of Drug Development 2004, p. 3).

Increased pharmaceutical product innovation was one of the key purposes of those decreases in drug development and regulatory review times, according to the pharmaceutical industry and governments who sought them, and the managers of regulatory agencies who adopted and implemented them in line with the demands of their political masters. For example, a report by the Charles River Associates (CRA) on behalf of the European Commission's DG Enterprise stated that the main purpose of accelerated evaluation/marketing provisions within the EU's supranational regulatory system and the increased the role of the EMEA in providing scientific advice to companies was to 'bring forward new products and increase the returns from truly innovative products' and 'act as a spur to innovation' (Charles River Associates 2004, p. viii).

This was confirmed in an interview with a European Commission official at the Pharmaceuticals Unit within DG Enterprise. As well as aiming to 'ensure a high level of health protection', the Pharmaceuticals Unit sought 'to support pharmaceutical innovation in the European Union and foster competition and transparency in the Community pharmaceutical market' (European Commission Enterprise Directorate-General 2000, pp. 4 and 5). As our interviewee explained, the view of DG Enterprise was that regulation should create an environment in which industrial innovation can flourish in order to yield important therapies for public health:

> You cannot disassociate public health protection from innovation ... If you think of public health promotion not just as *protection* but as *promotion,* then there are two sides to the coin. ... You have, on the one hand, to stimulate innovation in order to find the treatments for those incurable diseases *but* you have to balance it with tough regulation on the other hand, which has demanding data requirements in terms of proving safety, quality and efficacy. We don't see it as a conflict. And we clearly do see innovation as being a crucial role of regulation.[13]

In the US, encouragement of product innovation was also central to the reasons given for the introduction of accelerated regulation. The Senate report by the Committee on Labour and Human Resources, accompanying the 1997 FDAMA legislation, asserted:

> Increases in the time, complexity and cost of bringing new products to market are borne directly by the public, in delayed access to

> important new products – including life-saving medical therapies – and in higher costs. They are a growing disincentive to continued investment in the development of innovative new products and a growing incentive for American companies to move research, development, and production abroad, threatening our Nation's continued world leadership in new product development, costing American jobs, and further delaying the public's access to important new products (US Senate 1997, p. 7)

Yet, despite decreasing regulatory review times, provisions aimed at shortening development times, and increasing harmonization of regulatory science requirements in the EU and US (Kaitin and DiMasi 2000), there has actually been a *decline* in pharmaceutical product innovation since and during those neo-liberal reforms. We can see this by considering the number of innovative drugs (NMEs) that have been submitted to the FDA over time. Figure 2.2 shows that the number of NMEs submitted to the FDA for regulatory review fell from 45 in 1996 to 23 in 2010.

The falling numbers of innovative drug applications to the regulatory agencies have been mirrored by a decreasing number of approvals

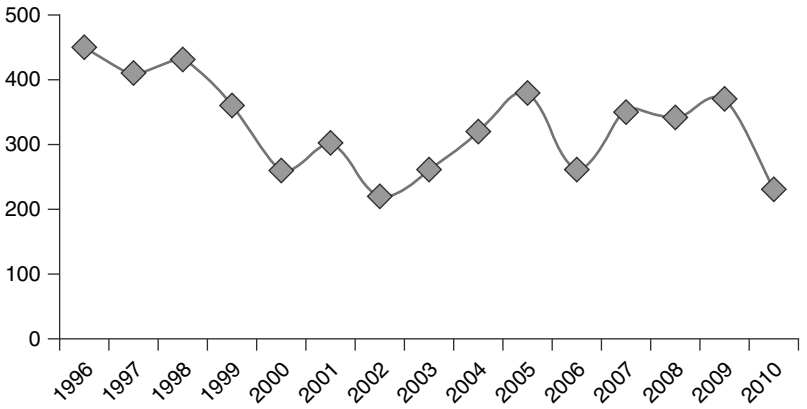

Figure 2.2 NME applications to FDA 1996–2010*

*2004–2010 represents application for new molecular entities filed under New Drug Applications (NDAs) and therapeutic biologics filed under Original Biologic Licence Applications (BLAs). 2001–2003 represents NMEs but not therapeutic biologics.

Source: FDA, 'Comparison of NMEs approved in 2010 to previous years'. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ucm242674.htm (Accessed 15 October 2011).

and market launches of pharmaceutical product innovations in the EU and US (Charles River Associates 2004; Turner 2004). In 2007, the FDA approved just 17 NMEs. This rose to 21 in 2008, but fell back to 19 in 2009. These figures were slightly higher than those for the mid-2000s, but still far behind the late 1990s and slightly less than the 22 approved in 2006 (Anon. 2008f). Similarly, EFPIA reported a decline in the number of NASs marketed in the region of Europe, falling from 89 between 1995–1999, to 57 in the period 2000–2004 (Anon. 2005d).

Indeed, by the mid-2000s, many commentators wondered whether the industry was facing a worldwide crisis in innovation (Centre for Medicines Research International 2002; 2005; Charles River Associates 2004; FDA 2004). Just 23 NMEs were launched on to the world market in 2004 – fewer than at any time in the previous 20 years (Centre for Medicines Research International 2005). The number of NDAs submitted to the centralized procedure saw a rise in 2004 of about 20 per cent over the previous year, but fell back to 2003 levels in 2005 (Anon. 2005e; 2006f). It rose again in 2006, but fell back again by 19 per cent in 2007 (Anon. 2008c). Overall pharmaceutical product innovation increased slightly in the late 2000s from its relatively very low level of the early/mid 2000s, but never returned to levels of the 1990s. Hence, the argument put forward by industry, neo-liberal governments and their allies in regulatory agencies – that accelerated regulatory review times and a more predictable regulatory environment was needed to stimulate pharmaceutical product innovation – finds no support in trends of product innovation since the mid-1990s.

As indicated by the quotations above from the US Senate (1997) and our informant at the Commission's Pharmaceuticals Unit, governments on both sides of the Atlantic attested not only that the neo-liberal measures to accelerate regulatory review, increase predictability in the drug development process, and require less test data from drug companies would stimulate pharmaceutical product innovation, they also proclaimed that by so doing, such measures would benefit patients and public health (Milne 2000). That view was made with increasing vigour by FDA management as the reforms progressed. Commenting on the effects of the 1992 accelerated approval regulations, PDUFA, and the priority review system for allocating resources, the FDA claimed that:

> To date, the agency has cut new drug approval times nearly in half, while the number of new drugs approved in a year has doubled…U.S. drug approval times have decreased dramatically and are now among the fastest in the world. Americans have access to new therapies

> faster, and, as a result, suffer less, recover more rapidly, are often cured completely, and live longer lives, or enjoy an improved quality of life. (FDA 1997a)

Similarly, at a public meeting on PDUFA in 2000, Janet Woodcock, the FDA's former director of CDER, declared:

> The public has received benefits from [PDUFA]. There is faster access to new therapies.... And ... there is increased industry incentive to direct attention into new therapeutic areas by the timeliness and the predictability of this program. (FDA 2000a)

As we explained in Chapter 1, there is no necessary correspondence between drug product innovation and therapeutic advance. The two phenomena are not entirely disconnected because without any drug product innovation, there would be fewer pharmaceutical therapeutic advances. However, neither should the two be conceptually fused because a drug may be an innovation without offering any therapeutic advance – as is clear from the FDA's own regulatory accounting. Accelerated review of 'me-too' drugs allocated standard review by the FDA might benefit industry but is likely to offer little or no benefit to patients. Conversely, in theory, it is possible that, while the overall number of NASs launched each year declined after the neo-liberal reforms, the number of NASs offering therapeutic advance could have remained constant or even increased. Hence, a partial decline in drug product innovation might not necessarily have any negative impact on public health. It follows that, to assess the validity of the claim that the neo-liberal reforms have led to an increase in the number of new drugs offering therapeutic advances and breakthroughs for patients, one must disaggregate the data on drug product innovation.

To do this, we must turn to the FDA because the EMEA does not publish data distinguishing between new drug products that offer modest or significant therapeutic advance ('priority' drug approvals) and those that offer little or no therapeutic advance ('standard' approvals). Figure 2.3 shows that from 1998 to 2010 the proportion of NME applications to FDA accorded priority review status has been fairly small. Significantly, Figure 2.3 reveals that *the number of new drugs offering therapeutic advance has also been in decline since 1998*.

In other words, the claims made by governments and regulators on both sides of the Atlantic that their neo-liberal reforms would lead to patients gaining faster access to more new drugs that they need is not

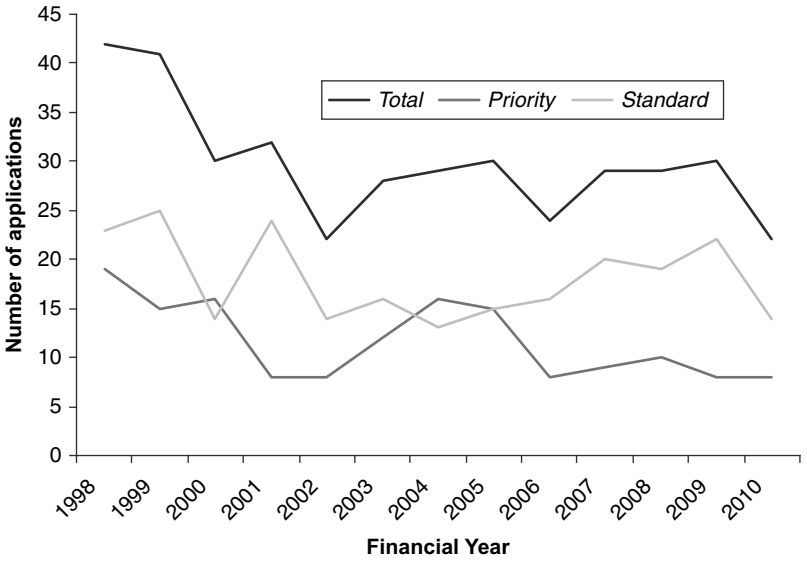

Figure 2.3 NME applications filed with FDA 1998–2010

Source: Compiled from FDA's annual PDUFA Performance Reports. Available at: http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/default.htm (Accessed 6 November 2011).

supported by the FDA's own quantitative evidence on the number of therapeutically valuable drugs going through the regulatory system. Moreover, the National Institute for Health Care Management (NIHCM) examined the number of therapeutic advances approved out of all the new branded medicines that entered the U.S. market between 1989 and 2000. The analysis included NMEs and 'incrementally modified drugs' (IMDs) – combinations or new formulations of existing pharmaceutical products on the market, but excluded biotechnology products. It was found that, between 1989 and 1994, out of a total of 350 NMEs and IMDs, the FDA approved 106 as priority drugs (30 per cent), but between 1995 and 2000, out of a total of 569, the agency approved only 133 as priority drugs – a decline to just 23 per cent (National Institute for Health Care Management Foundation 2002, p. 10). Subsequently, the report by Charles River Associates signalled similar conclusions, finding that about 20 per cent of NDAs approved between 1990 and 1994 were accorded priority reviews, compared with about 15 per cent between 2000 and 2003 (Charles River Associates 2004, p. 36).

Although equivalent data are not available from the EMEA, it is likely that similar trends will have occurred in Europe as there is a considerable overlap between drugs approved by the FDA and drugs approved via the EU's supranational centralized procedure (Charles River Associates 2004, pp. 29–32). Independent evaluations of the therapeutic value of drugs approved via the centralized procedure suggest that, as in the US, the proportion of new pharmaceutical products that represent significant therapeutic advance is small. Garattini and Bertele (2001, p. 65) judged that of the 126 products approved by the CPMP in its first year, only 60 could be regarded as offering any therapeutic advance. With respect to some specific disease categories these authors found that, of the nine mind-altering drugs approved through the EU's centralized procedure between 1995 and 2002 only one offered a therapeutic advance, and the 11 cardiovascular drugs approved during the same period 'contributed little to recent progress in the cardiovascular area' (Garattini and Bertele 2003a; 2003b). In direct contradiction with the assertions made by the architects and managers of neo-liberal regulatory reform in Europe, Garattini and Bertele (2003b, p. 706) reported:

> These agents seem to follow the logic of obtaining a share of large market areas rather than attempting to cover any unmet patient needs. Interestingly ... the new drugs usually cost more than similar drugs already available, even if they are only equivalent in terms of efficacy and safety.

In addition, the French-based medical/healthcare professional organization, Prescrire, judged that, of the 18 innovative drug products approved through the EU centralized procedure in 2000, none represented major therapeutic advance, three offered an advantage but not in a way that would fundamentally change therapeutic practice, and three had minimal additional therapeutic value, 11 offered no therapeutic advance, and one could not be evaluated (Anon. 2001c).

Overall, the evidence suggests that the number of new drugs offering modest or significant therapeutic advance in the EU and the US represents a minority of pharmaceutical product innovations, and evidence from the US indicates that this percentage has fallen during the period characterized by neo-liberal regulatory reforms. It is not that the pharmaceutical industry's research activity had declined because between 1980 and 2005, the number of pharmaceuticals in R&D increased threefold (Anon. 2005f). Rather, it was that R&D did not yield many new drugs offering significant therapeutic advance.

The research-based pharmaceutical industry argues that organizations like Prescrire place too much emphasis on innovative drugs that offer modest or significant therapeutic advantage and neglect the positive contributions of the other pharmaceutical product innovations that promise little or no therapeutic advance – 'standard drugs' in FDA terms, though often referred to as 'me-too' drugs because they are so therapeutically similar to medicines already on the market. In particular, the industry contends that me-too drugs create market competition, which leads to cost benefits and lower prices for patients and healthcare systems (EFPIA 2000, p. 19). Furthermore, the industry is joined by some regulators in claiming that, even if a new drug cannot be shown to offer any specific advantage over existing therapies in clinical trial populations, it may still offer an advantage to some individual patients (EFPIA 2000, p. 20).[15,16] Whatever, the merits of such arguments in favour of me-too drugs, we note that the evidence we have presented in this section demonstrates that pharmaceutical product innovation, as a whole, including me-too drugs, declined after neo-liberal reforms, presumably shifting any benefits associated with me-too drugs into decline also.

Nonetheless, in order to fully appreciate the public health implications of the fact that, despite over 20 years of regulatory reforms ostensibly aimed at accelerating pharmaceutical innovations needed by patients, only a minority of pharmaceutical product innovations offer even modest therapeutic advance, and fewer still promise significant therapeutic advance, it is important to consider these claims about the *indirect* benefits from me-too drugs. The assertion that me-too drugs provide a sensible mechanism for reducing pharmaceutical prices is not plausible. In Europe, some regulators told us that pharmaceutical companies use approval of an innovative drug through the centralized procedure as a justification for charging a very high price, even if the product offers little or no therapeutic advance.[17,18] Regarding cancer drug innovations approved during the first six years of the centralized procedure, Garattini and Bertele (2002) found that those drugs were much more expensive than existing therapies despite an absence of proven therapeutic advantages. Meanwhile, in the US, the NIHCM reported that the average price per prescription in 2000 for a standard NME (me-too) was twice that of a drug approved before 1995, implying that having innovative pharmaceutical products made up of largely me-toos has done little, if anything, to bring down American drug prices (NIHCM 2002, p. 13).

Regarding the possibility that a new drug showing no therapeutic advance in clinical trials may nevertheless provide such benefits to

individual patients, one cannot entirely discount such hope, but it is rarely evidence-based. There is hardly ever data from clinical trials identifying subsets of patients with particular characteristics that might derive additional therapeutic benefit when a drug shows no overall therapeutic advance. Consequently, physicians must somehow work that out for themselves in clinical practice, selecting optimal treatments out of a range of therapeutic options for patients on the basis of individual observation. Yet such a process renders almost impossible verification of any therapeutic advantage me-too drugs may or may not provide and, unlike controlled trials, cannot be a basis for generalization beyond the individual patient to evidence-based medicine or regulatory decision-making.[19,20]

Such hope and wishful thinking about the therapeutic value of me-too drugs can, however, be the basis for pharmaceutical promotion, which may act as a substitute for scientific evidence. According to Kessler *et al*. (1994), the competitive sales behaviour of drug companies in medical fields crowded with me-too drugs has led to misleading promotion, increased healthcare costs and inappropriate prescribing, rather than patient benefits. It is claimed that pharmaceutical companies may use 'seeding trials' to make unsubstantiated claims about the superiority of their me-too drugs and run 'switch campaigns' to persuade doctors to change their patients' medication to the new me-too drug. Such promotional practices may be aided by, and reinforce, an irrational ideology that 'new' must be better (Kessler *et al*. 1994).[21]

So far in this section, we have discussed the macroscopic effects (or lack of effects) of neo-liberal regulatory reform on the stimulation of pharmaceutical product innovation and the provision of innovative pharmaceuticals that offer therapeutic advance for patients and healthcare. Scholars typically consider the impact of regulation on pharmaceutical innovation, but often neglect the effects of innovation rates on drug regulation. Since the neo-liberal reforms, such neglect can no longer be countenanced because, as we have seen, regulatory agencies in European nations, the supranational EU, and the US depend so heavily for their funding on industry fees. Consequently, the declining number of innovative drug applications has had a serious impact on the resources of regulatory agencies.

Earlier in this chapter, we explained how PDUFA caused a redistribution of resources away from some public health protection activities because of the renewed emphasis on the new drug review process. Declining numbers of NDAs and associated fees to pay for staff can only have accentuated resource problems throughout the agency. It has also

had a serious impact on EMEA's regulatory activities. The crisis of 2002 is just one example. Reporting on planned new EU directives, IMS Health (2003) observed:

> The EC moves come at a time of increased concern on both sides of the Atlantic about perceived dips in output from pharmaceutical industry pipelines. Indeed, in Europe the EMEA is facing a financial crisis due to a dramatic drop in new drug applications. The number of applications fell from 54 in 2000 and 58 in 2001 to just 31 in 2002.

A commentary in the pharmaceutical trade press, *Scrip*, captured well the nature and implications of the crisis:

> On 3 October, the EMEA announced that only 25 new drug applications had been received by the end of September, down from 58 for 2001 as a whole. If orphan drug applications are stripped out of the figures, the number was 14, compared with 46 for the entire previous year. The EMEA has expected 50 new drug applications (excluding orphan products) this year. As the agency receives 80 per cent of its income from industry fees and the fees are highest for new chemical entities [NMEs], the application decline has forced the EMEA to make emergency savings such as delaying recruitment and cancelling working groups. (Anon. 2002f)

Consequently, the CPMP had to cancel expert group meetings on drug efficacy, vaccines, paediatrics, and the quality of regulatory documents (EMEA 2002a).

Risk management

In the late 1990s, senior FDA and US government officials began to articulate and practice an explicit risk management strategy for pharmaceutical regulation (FDA 1999a). The official rationale behind this strategy was that the management of pharmaceutical risks should be optimized by monitoring drug products throughout their life-cycle so that risks could be better foreseen and tailored to more nuanced regulatory interventions and patient sub-populations, thereby minimizing shocks to the medical system caused by withdrawing drugs from the market. The FDA's embrace of risk management policies was officially in response to a large number of high-profile drug products being withdrawn from the US market on safety grounds in the mid and late 1990s.

Insofar as that is an accurate explanation for the FDA's introduction of risk management policies, it also provides a superficial understanding because one must ask why that significant rise in drug safety withdrawals in the US occurred. It was not by chance (US GAO 2002). It was structurally related to the deregulatory reforms put in place during the 1980s and 1990s, which not only accelerated the pre-market review of new drugs, but also permitted more questions about safety (as well as efficacy) to be answered in the post-marketing phase, due to less demanding standards of pre-approval evidence. Olson (2002) has provided some of the most compelling evidence linking the 1992 deregulatory reforms of PDUFA and the 'accelerated approval' rules to drug safety problems. By analysing the ADRs recorded in the FDA's Spontaneous Reporting System (SRS) for 141 innovative pharmaceuticals (NCEs) approved on to the market by the agency between 1990 and 1995, she found that the reductions in new drug review times, which occurred in that period, were significantly associated with increases in both ADRs requiring hospitalization and ADRs resulting in death.

Hence, the emergence of risk management as a response to drug safety withdrawals was also largely an effect of neo-liberal deregulatory reforms. Indeed, there is evidence that risk management was also itself an expression of pro-business, neo-liberal governance of drug safety problems. Concerned about public confidence in the pharmaceutical industry and drug safety regulation, the pressure for risk management policy was also driven by the pharmaceutical industry and a strongly neo-liberal Republican-controlled Congress, as well as the FDA. As several of our FDA informants explained:

> The first time I can recall hearing about risk management [within the FDA] was 1997. It [risk management] was a reaction to a fairly large number of withdrawals in a short period of time and the agency [FDA] getting pressure from Congress – they represent industry if a drug company is in their district. There was also direct pressure from industry.[4]
>
> We saw it [risk management] in the negotiations for the re-authorization of PDUFA. Companies were getting nervous about the number of drugs coming off the market and they wanted the standards raised [i.e. more difficult] to call an adverse drug reaction 'an adverse drug reaction'. And they wanted something to [re]assure the public – I think the FDA maybe also did – that everything was being done. The agency had taken a lot of criticism and was getting sensi-

> tive to drug withdrawals, so they tried to raise the profile of looking at drug risk.[6]
>
> The drug industry was behind other industries in bringing the concepts of risk management into practices. So that was part of it, and highly publicized examples of problems with drugs that people felt in retrospect could have been avoided if we'd thought more about what could happen in advance.[22]

Hence, the idea of pharmaceutical risk management policy originated in the US, but it migrated to Europe. According to Demortain (2008) the 'crisis' over the safety of the lipid-lowering drug, cerivastatin, in the late 1990s and early 2000s in Europe led to an official consensus at least about the idea of pharmaceutical risk management across most western countries, culminating in an internationally agreed guideline on 'pharmacovigilance planning' at the ICH. By 'pharmacovigilance planning' was meant a plan for each new drug product detailing how possible adverse effects could be detected, understood, monitored, assessed, and perhaps even prevented. Although that was the official representation of risk management policy, some experts took an altogether more sceptical view of it, suggesting rather less consensus among regulatory agencies. In 2005, one European regulator told us: 'Risk management is an invention of industry to say that you can keep a drug even if it is toxic, if you know how to manage risk'.[12]

In the same year, Horst Reichenbach, the European Commission's director-general for enterprise, stated that the Commission was looking into whether the EU's 2004 pharmaceutical legislation was sufficient to reduce the 'risk' of product withdrawals over safety issues in the future. The implication being that the 'risk' to be managed was the risk of product withdrawal, with the risk of the product itself receiving secondary consideration. Reichenbach also linked the EMEA's conditional marketing provisions with the introduction of risk management plans, noting that, at the time of marketing approval, one cannot know the full safety profile of a new drug (Anon. 2005g). In other words, risk management plans were particularly prevalent among innovative pharmaceuticals accelerated on to the market by various deregulatory measures in the EU (Anon. 2005h). Indeed, since the mid-2000s, risk management and pharmacovigilance planning are often connected with the goal of faster drug development times within pharmaceutical policy discussions (Anon. 2006g).

In 2005, the EMEA formalized the EU's risk management plans as the 'European Risk Management Strategy (ERMS)' (Anon. 2005i). Within

this framework, as in the US, pharmaceutical manufacturers may be required by regulators to submit a risk management plan to track the use of the new product on the market, along with the new drug application, though, in the US, this is known as 'Risk Evaluation and Mitigation Strategy (REMS) (Anon. 2006h; Anon. 2007c). While risk management in the US owes its origins to deregulatory reforms and associated drug safety withdrawals in the late 1990s, its development was also affected by the very public drug disaster caused by the arthritis medication, *Vioxx*, in 2004, which was estimated by FDA safety officers to have caused over 80,000 heart attacks or strokes in the US alone, with a mortality rate of 30–40 per cent (Light 2010, p. 12).

After Vioxx, arguably the worst drug disaster in the history of the US, the FDA commissioned the National Academy of Science's Institute of Medicine (IoM) to provide recommendations on how to improve drug safety, which, in turn, influenced a Congress increasingly animated by drug safety concerns in the aftermath of Vioxx. The IoM (2007) report recommended that the FDA's regulatory authority over drug safety needed clarification. In the same year, an FDA report found that drug companies had failed to even start 65 per cent of the 1200 post-marketing safety studies requested by the agency (Anon. 2008f, p.26). In response, Congress passed the 2007 FDA Administration Amendments Act (FDAAA), which authorized the agency to proactively require pharmaceutical firms to conduct studies of drug risks with the power to impose fines up to US$10 million dollars on companies that failed to comply. In truth, the FDA always had the power to request such studies, but had not enforced it. The FDAAA sent a clear message that the FDA should give more attention to drug safety pursuits and enforcement, including a re-authorization of PDUFA enabling the agency to use industry fees to improve the drug safety system (Anon. 2008f, p.26). Such developments accentuated the role of risk management and REMS in particular because the focus of the IoM and FDAAA was post-marketing safety studies and evaluation (Anon. 2008g).

Consumerism and the patient–industry complex

No organizational analysis of the neo-liberal period of pharmaceutical innovation and regulation since 1980 would be complete without some consideration of the growth of 'consumerism' and the 'patient–industry complex'. By 'consumerism' here, we are not referring to consumer advocacy to protect public health, but rather the ideology and movement regarding patients as 'consumers' in a marketplace actively

seeking pharmaceutical treatments. As disease-politics theorists, such as Carpenter (2004) and Daemmrich (2004), have noticed, AIDS patient activism in the US fuelled an increase in such consumerism. However, American pharmaceutical consumerism can also be traced back to deregulatory reforms at the FDA, whose conceptualization pre-dated AIDS.

In 1982, FDA Commissioner Hayes predicted a rise in advertising of prescription drugs directly to patients, as well as the established advertising to physicians. Advertising prescription drugs to physicians, rather than patients, had long occurred precisely because such drugs could only be taken by patients on prescription, so the doctor, not the patient, was regarded as responsible for selecting the appropriate medication. The idea of advertising prescription drugs directly to patients, bypassing doctors, in effect, treated patients as consumers. Indeed, such advertising became known as 'direct-to-consumer advertising' (DTCA) of prescription drugs. Hayes attributed potential growth in DTCA to patients demanding a greater role in selection of their health care products, though advertising could only occur if it was profitable for would-be advertisers.

At that time, the US pharmaceutical industry was not particularly enthusiastic about DTCA of prescription drugs, so it seems unlikely that the FDA was responding to industry pressure on this issue in the early 1980s (US House of Representatives 1984). Indeed, historically, the claim by the research-based firms that they produced solely medical drugs for the medical profession and did not flirt with the fancies of the general public was how that part of the industry defined itself as 'ethical' (Abraham 1995a, p. 39). Political movements emphasizing citizens' rights from the civil rights campaigns of the 1960s to the environmentalist and feminist organizations of the 1970s certainly ignited an 'active citizenship' more inclined to reflect critically on its relationship with government and other powerful bodies in society, including the medical profession and the pharmaceutical industry (Abraham and Lewis 2002). Witness the creation of the environmentalist and public health advocacy organization, known as 'Public Citizen', in the US in 1970. Some scholars have considered those developments to be so fundamental that they have ascribed them the status of a social transformation, known as 'reflexive modernization' (Beck 1992).

Yet, although those movements asserted their rights to be more informed and pro-active in matters affecting their lives and their bodies, it is much less clear that they were demanding more 'information' in the form of advertising. Even if one accepts the broadly plausible theory that, as one entered the 1980s, modern society was transforming into one with many more reflexive, rather than passive, consumers, there

is no necessary connection between such reflexivity and a demand for advertising. The link was made by FDA Commissioner Hayes because he chose to make it. He fused active citizenship and consumer reflexivity with a neo-liberal ideology of consumerism commensurate with demand for advertising that was consistent with the neo-liberal political aspirations of the incumbent Reagan Administration.

Given the lack of enthusiasm among the US pharmaceutical industry for DTCA of prescription drugs, in 1982, the FDA requested a voluntary moratorium, calling for a period of cautious restraint by would-be advertisers. However, in 1985, the agency withdrew its moratorium on the grounds that the existing regulations on advertising were sufficient to protect consumers. Some commentators argue that this lax approach to regulation was not intended to open the floodgates for DTCA in the US, but rather was recognition by the FDA of a new trend in society (Pines 1999). Yet that analysis begs the question why the societal trend of reflexive modernization was interpreted as a demand for advertising in this context. We contend that that is best explained by the influence of deregulatory neo-liberal political ideology gaining ascendancy at that time. Significantly, the FDA lifted its moratorium on DTCA at the request of the DHHS and Reagan's White House Office of Management and Budget (Anon. 1993b).

With the lifting of the moratorium, the industry could not resist the lure of sales and profits resulting in a considerable increase in American pharmaceuticals firms' spend on print advertising, reaching US$12 million on DTCA in 1989. However, the US regulations on 'fair balance' and 'brief summary' made DTCA cumbersome for the broadcast media. In 1997, by which time the pharmaceutical industry had become firm supporters of DTCA, even those restrictions were relaxed so that broadcasting product advertisements merely had to provide consumers with access to the drug's official labelling via a telephone number, a webpage, a concurrent advertisement, or additional information from pharmacists, physicians or other healthcare providers (Conrad and Leiter 2008). The consequence of these deregulatory measures in 1985 and 1997 was that expenditure on broadcast DTCA, a form of prescription-drug promotion which bypassed doctors, grew almost 80-fold in the US, from US$55 million in 1991 to US$4.2 billion in 2005 (UG GAO 2006).

From the early twentieth century, pharmaceutical firms have sought to develop relationships with doctors in order to promote their products. However, in the US, during the late 1980s and early 1990s, the apparent success of AIDS patient activism in influencing some FDA decision-making combined with the growth in DTCA, persuaded drug companies

that it could be profitable to forge much more extensive collaborations directly with patients. Organizationally, the most amenable tactic was to develop working relationships with patient groups, often funding them. Such funding has become an increasing trend in the last decade (O'Donovan 2007). For example, the pre-eminent American advocacy group for people with ADHD is 'Children and Adults with Attention Deficit/Hyperactivity Disorder (CHADD), 22 per cent of whose revenue in 2004–2005 came from the pharmaceutical industry (Phillips 2006, p. 434). While the precise effects of pharmaceutical firms' financial support on patient groups is difficult to gauge, such close associations are clearly important to the industry as an additional pathway, beyond doctors, for creating 'consumer demand' for their products (Herxheimer 2003). In a survey of US executives from 14 pharmaceutical companies, 75 per cent of respondents cited 'patient education' as the top-ranked marketing activity necessary to bring a brand to 'the number one spot' (UK House of Common Health Committee 2005, pp. 74–6). Collaborations of this kind are emerging as, what we call, a 'patient–industry complex'.

While in the US, the 'patient–industry complex' has centred around FDA decision-making, in European countries much of the focus has been on access to drugs within national healthcare systems after marketing approval. Nonetheless, the principal modus operandi of industry–patient group collaboration, learned by American pharmaceutical firms, and enabled by a neo-liberal ideology of consumerism in the EU and the US, has been basically the same. For example, in the UK, of most significance has been patient access to new drugs on the NHS, which pays the full cost of drug treatment provided that the appropriate NHS authorities approve funding. The National Institute for Health and Clinical Excellence (NICE), which assesses the cost-effectiveness of many new drugs for use in the NHS after they have been granted marketing approval by UK drug regulatory authorities, makes key recommendations about whether many new drugs should be made available on the NHS. The significance of the patient-industry complex in the European setting is well illustrated by NICE's experience with recent drugs developed to treat Alzheimer's disease.

In March 2005, NICE recommended that four drug treatments approved to treat Alzheimer's (Aricept, Exelon, Reminyl and Ebixa) should not be funded by the NHS because they were not cost-effective. However, following a high profile campaign in the media and a formal appeal involving patient groups, such as the Alzheimer's Society, NICE revised its guidance to allow NHS funding of the drugs for people

with moderate stages of the disease, but still not those with early-stage Alzheimer's. The Alzheimer's Society then took NICE to the courts, which ultimately insisted that NICE should investigate ways of making the drugs available to all those with the disease. Notably, the manufacturers of those Alzheimer's drugs were the lead claimants in the court case and centrally involved in the formal appeal to NICE (BBC News24 2007).

As we have discussed, neo-liberal ideology and its associated deregulatory politics emerged powerfully from the early 1980s in many European countries, just as in the US. However, DTCA of prescription drugs remained banned in Europe throughout the 1980s and 1990s. In the supranational EU, the socio-political roots of efforts to legalize DTCA are much more clear-cut than in the US probably because, by the early 2000s, when those efforts got underway in earnest, neo-liberal ideology was more established and the pharmaceutical industry had become a strong supporter of such advertising. Indeed, in the early 2000s, the pharmaceutical industry, with support from the European Commission's DG Enterprise, campaigned vigorously for the legalization of DTCA in the EU.

Advertising per se is not the concern of this book. However, the nature of the DTCA campaign in the EU is highly instructive in revealing the relationships between deregulatory politics and the neo-liberal ideology of consumerism, which are part of the context of drug innovation and regulation more generally. In that respect, it shares much in common with the campaign to introduce FDAMA in the US in 1997.

Although patient groups were not initially prominent in the campaign, its promoters from industry and DG Enterprise characterized patients as consumers able to decide which drugs were best for them without doctors' supervision. The campaign utilized a discourse of 'the informed patient' and the 'expert patient'. To be sure, doctors' failure to adequately inform patients about prescription medicines can be a significant problem (Britten 2008), but it was an unsubstantiated leap of faith to assume that pharmaceutical companies would fill the gap left by doctors in that respect. In addition to the use of such discourse as an ideological lever with which to achieve deregulatory goals, the industry viewed its organizational links with patient groups as a material resource with which to advance the dismantlement of DTCA bans.

The UK research-based pharmaceutical industry led the way in the European campaign, probably because London is home to the EMEA. Quoting from a speech by the Director-General of the Association of the British Pharmaceutical Industry (ABPI), Medawar and Hardon (2004, p. 121) report that the 1998 'Informed Patient Initiative' was the first

part of the industry's 'battle plan'. The second part was the ABPI's publication, 'The Expert Patient', which according to the Director-General, was 'part of a softening-up assault to be mounted through those interested parties and opinion leaders by stimulating debate'. Evidently, the purpose of the campaign was to promote a consumerist ideology of patient self-care and self-medication in order to create a basis for arguing that patients were sufficiently knowledgeable to evaluate advertising claims about powerful prescription drugs. As the following passage from an article published in *Pharmaceutical Marketing* suggests, the industry hoped that the creation of such consumerist ideology would be sufficient to compel European regulators and governments to legalize DTCA throughout the EU:

> The ABPI battle plan is to employ *ground troops in the form of patient support groups*, sympathetic medical opinion and healthcare professionals which will lead the debate on the informed patient issue. This will have the effect of weakening political, ideological and professional defences. ... Then the ABPI will follow through with high-level precision strikes on specific regulatory enclaves in both Whitehall and Brussels. (Jeffries 2000, quoted in Medawar and Hardon 2004, p. 121, emphasis added)

In fact, that campaign by the industry and DG Enterprise was unsuccessful. Many EU public health organizations, medical professionals, and some national government health agencies opposed relaxation of the ban, underlining the crucial role of health professionals in the provision of tailored information to patients, and pointing to the practical difficulties of regulating and enforcing the distinction between 'information' and 'advertisement' (Association Internationale de al Mutualite et al. 2009). Consequently, to date, the European Parliament has refused complete legalization of DTCA, concluding that it would not be in the interests of patients' health. However, there are signs that the European parliament may permit the pharmaceutical industry to provide some restricted and circumscribed 'information' about their products directly to consumers via some media.

While the pharmaceutical industry and the European Commission have keenly emphasized the importance of product information provided by companies to consumers, drug regulation in Europe has been slow to develop and implement citizens' legal rights to information more broadly, compared with the situation in the US. After a drug has gained marketing approval in the US, citizens may gain

extensive access to regulatory documents underpinning the approval decision under the 1967 Freedom of Information Act. In addition, FDA expert advisory committees are generally held in public (Jasanoff 1990, p. 247).

By contrast, as recently as 1995, the EMEA established only discretionary transparency in the form of European Public Assessment Reports (EPARs) for each drug approved via the centralized procedure. In the EPARs, EU regulators provided a summary basis of the approval decision, but citizens had no right to demand information beyond that. It was not until EU Regulation 726/2004 that, in principle, EU citizens could request all documents underpinning EMEA decisions, subject to restrictions regarding commercial confidentiality, which were defined broadly as any information that would harm the interests of pharmaceutical companies (Anon. 2006b). However, in practice, the EMEA has been tardy to respond to requests for information and overly protective of companies' commercial interests (La Revue Prescrire, 2009). In June 2010, the EU Ombudsman publicly accused the EMEA of maladministration after finding that the agency had refused to release information to academics on grounds of commercial confidentiality when the documents requested did not contain commercially sensitive information. Subsequently, the EMEA finally released the information – *four years after the initial request* (Gotzche and Jorgensen 2011).

Thus, not only has the campaign for advertising information directly to consumers reflected industry interests, but so too has the European Commission's focus on selective provision of information by companies, rather than concentrating on more rapidly widening citizens rights of access to information about pharmaceutical products in the EU.

Conclusion

AIDS patient activism in the US has frequently been credited in publications, conferences, and regulatory thinking with transforming the orientation and philosophy of the FDA during the late 1980s and early 1990s. In part, this may be due to an unintended effect and misunderstanding of works, such as that by Epstein (1996), who himself never made such claims. For some regulators it may be partly explained by a rationalization that is more comfortable than the alternative, namely that the FDA's mission to protect public health was compromised by various pro-industry interests in government and business.

Whatever the reasons for the popularity of that mistaken view, the forgoing analysis demonstrates beyond doubt that AIDS activists were

but one part of a wider convergence of pressures affecting FDA policy and regulatory science at that time. While AIDS activism *and* the exigencies of the AIDS crisis itself undoubtedly caused the FDA to accept a greater degree of uncertainty in its risk–benefit assessments of the first AIDS treatments, it is highly unlikely that such lowering and loosening of standards for drug approval would have been formalized into new regulations, or extended to non-life-threatening diseases, had it not been for the interventions of the pharmaceutical industry and its allies within the Reagan and Bush Administrations. The AIDS treatment activists advocated 'a very limited program accessible only in life-threatening situations' and were significant in bringing about regulatory acceptance of CD4(T) cell counts as a surrogate marker of HIV/AIDS in 1991 (Epstein 1997, p. 702). Yet, that 'limited' goal was extended by the 'Subpart E' regulations in 1988 to 'severely debilitating' diseases, and then by the 'Subpart H' regulations in 1992 to 'serious' diseases (FDA 1998a, p. 4).

In particular, the President's Task Force on Regulatory Relief, followed by Quayle's White House Council of Competitiveness exerted continual pressure on the FDA throughout the 1980s and into the early 1990s to 'streamline' the drug approval process for the benefit of industry. As well as proposing accelerated approvals, Quayle's Council proposed a new 'flexible efficacy standard' whereby FDA would make a deliberate effort to 'interpret the statutory requirement of efficacy in a manner that maximizes a drug's potential for approval' and a hiring strategy with a commitment that all new staff hired should be dedicated to the drug approval process until the goals for approval times were met (Anon. 1991j) As we have seen, the primary goal of the Quayle Council, and the Task Force on Regulatory Relief before it, was to lever the FDA into implementing measures that would remove regulatory barriers to the pharmaceutical industry's access to markets for its products.

The demands of the AIDS activists for weaker regulatory standards to expedite approval of AIDS drugs in the late 1980s and early 1990s provided public legitimation and FDA rationalization for that goal, as patients themselves appeared to be asserting a coincidence of interests between industry and patients' health. As we have shown, the nature of the regulatory relationship between the FDA and industry had already shifted considerably before the AIDS crisis. Nonetheless, AIDS activists' demands strengthened the arguments of those who advocated a more co-operative relationship between industry and the FDA – if all parties shared an interest in expedited drug development and review, then conjuring a logic that all parties should work together as 'partners' became easier.

In contextualizing and explaining the role of AIDS activism, it is also important to note that the demands of the AIDS treatment activists for specific FDA 'reforms' were themselves shaped and circumscribed by external realities that cannot be reduced to a simple reflection of 'patient interest'. Early activists' demands for conditional approvals were in part determined by a situation in which pharmaceutical companies controlled all information about, and patient access to, investigational drug products. Arrangements designed to allow patient access to investigational drugs, known as 'expanded access programmes', existed before FDA reform, but depended on companies' willingness to set up such programmes. Arguably that asymmetry in power and control was at the root of what needed to be reformed. Expanded access programmes offered only weak commercial incentives to manufacturers. Aware of that, the activists sought earlier *marketing* approval (conditional approval) for AIDS drugs. As Epstein (1997, p. 702) puts it:

> Conditional approval, by contrast, was designed with the explicit goal of enlisting the pharmaceutical companies by giving them a chance to do what they liked best: earn profits.

Furthermore, it is possible that AIDS activists miscalculated the real interests of public health at that time. In subsequent years, with hindsight, some of the prominent activists from that period have expressed the opinion that they were wrong to demand earlier access to drugs whose benefit and safety had not been established (Hilts 2003, pp. 304–5). For instance, Gregg Gonsalves, of the AIDS Treatment Action Group, stated:

> We have arrived in hell. AIDS activists and government regulators have worked together, with the best intentions, over the years to speed access to drugs. What we have done, however, is to unleash drugs with well-documented toxicities onto the market, without obtaining rigorous data on their clinical efficacy. (cited in Hilts 2003, p. 251)

One may confidently conclude that it would be inaccurate to suggest that changes in the philosophy and practice of pharmaceuticals regulation in the US, which occurred throughout the 1980s and the 1990s, resulted solely, or even mainly, from the demands and activities of the early AIDS activists or patients' demands more generally. Expedited development and review was just one example of a number of

measures intended to speed the marketing of *all* new drugs, regardless of whether they offered therapeutic advantage to patients. Moreover, analysis of events leading up to the 1997 FDAMA indicates that pressure for those legislative reforms came not from patients, but from industry and neo-liberal ideology in Congress. In fact, many patient groups, including AIDS activists, opposed the bulk of FDAMA reforms. In these respects, disease-politics theory has been built on flawed foundations, and its proponents have been mistaken to think that it forms the central dynamic of regulatory politics in the pharmaceutical sector, even in the US.

In Europe, the central role of neo-liberal political influence in government together with the interests of the pharmaceutical industry in shaping drug regulatory reform since 1980 is much more clear-cut than in the US. Patient activism demanding accelerated approval of new drugs in Europe was rare during the neo-liberal reforms of the 1980s and 1990s. Although it has grown in the 2000s within Europe, it has been primarily aimed at gaining access to drugs within the healthcare systems of *individual European countries after marketing approval* by EMEA or a national regulatory agency. Hence, insofar as patient activism had become significant within Europe in the 2000s, it cannot account for the neo-liberal framework that shaped the emergence of supranational EU pharmaceutical regulation during the 1980s and 1990s. Nor can it explain the deregulatory measures adopted during the last decade to accelerate drug development and approval at the *supranational EU* level. Rather, those developments were driven almost entirely by a pro-industry neo-liberal political agenda. One would be hard-pressed to find any patient or consumer group in the EU or the US that supported or demanded increased dependence of drug regulatory agencies on industry fees.

Quite distinct from the historical question of what role patient activism actually played, there is the sociological matter of how patients' interests have been *represented by others* in relation to political change. Regulatory reforms in the US and, subsequently in the EU, to accelerate drug development and review were justified by government agencies on the basis of patients' 'expectations' and the public health benefits claimed to accrue from faster approval of innovative drugs. For instance, the Prescription Drug User Fee Amendments of 2002 (PDUFA III) stated:

> The Congress finds that prompt approval of safe and effective new drugs and other therapies is critical to the improvement of the public health so that patients may enjoy the benefits provided by these

> therapies to treat and prevent illness and disease. (PDUFA 2002, section 502)

The achievement of such ideological representation was also bolstered by the organizational strategies of the pharmaceutical industry, especially in forging the emergence of the patient-industry complex, and the discourses of the 'expert patient' and the 'informed patient'. All of these served as levers with which to create the impression that the commercial interests of industry coincided with advancement of patients' health, and that weakening regulatory standards was a liberatory development in the best interests of patients. Yet, the evidence suggests overwhelmingly that both PDUFA and FDAMA were designed to, and have increased, the FDA's responsiveness to industry interests, while the number of innovative pharmaceuticals offering modest or significant therapeutic advance to patients has gone into decline.

Similarly, promoting the interests of the drug industry was a predominant concern of the European Commission's DG Enterprise with responsibility for pharmaceuticals regulation in the EU, and also apparently the management of the EMEA.

By contrast, tracking the extent to which new drugs offered therapeutic advance for patients together with provision of publicly accessible information about whether the development of such drugs was increasing or going into decline proved to be a much lower priority for EMEA and the European Commission. Rather, the 2004 legislative review of EU pharmaceutical regulation took place in the context of increasing concern at the Commission that the European drug industry was losing competitive ground to the US (Gambardella *et al*. 2000, pp. 83–4). Concerns about enhancing the environment for pharmaceutical innovation, manufacture and sale were perceived as the primary goals underlying the draft legislation.

In this chapter, we have shown that, at the level of social and political organization, the vast majority of the deregulatory reforms of the neo-liberal era to accelerate drug development and approval were neither demanded by patients nor primarily motivated by patients' interests. Despite misleading representations to the contrary, the goal to stimulate pharmaceutical innovation was not necessarily in patients' interests because most innovative drugs offered little or no significant therapeutic advance. Furthermore, we have shown that, irrespective of the motivations and ideological representations behind the deregulatory reforms, the number of innovative pharmaceuticals offering modest or significant therapeutic advance actually went

into decline after those reforms. Such findings certainly provide no evidence to support the claims of neo-liberal theory that the deregulatory reforms were, across the pharmaceutical sector as a whole, in patients' health interests. Indeed, our macro-political findings suggest that the neo-liberal reforms have undermined the capacity of pharmaceutical regulation to promote and protect the best interests of patients and public health.

Rather, the pharmaceutical industry has gained privileged access to the state in the neo-liberal era and worked in collaboration with its allies in the executive and legislative branches of government to bring about regulatory reforms in its commercial interests. This has made it possible for the industry and government to work together on a pro-business deregulatory agenda, including reforms of drug regulatory agencies themselves, such as appointments of more industry-friendly heads of the drug regulatory agencies, increased dependence of the agencies on industry fees, extension of informal consultation between regulators and firms, and responsiveness to commercial, rather than health priorities in terms of how quickly regulatory review of new drugs is completed. Such neo-liberal corporate bias has often operated via legislation beyond the regulatory agencies. However, throughout the neo-liberal reforms, including even the alteration of the FDA's mission statement in the FDAMA legislation, the regulatory agencies in both the EU and the US have maintained their mandate to promote and protect public health. In that context, many of the reforms to the drug regulatory agencies put in place as a result of the corporate bias during the neo-liberal period have made the agencies more vulnerable to capture by the interests of industry.

Although there are certainly differences between the evolution of pharmaceutical regulation in the EU and the US in the neo-liberal era, they are heavily outweighed by convergences between the two regulatory systems. Two phases of convergence can be identified. Initially, during the 1980s, corporate bias was much more developed in Europe than in the US, as reflected by the extent to which European drug regulatory agencies were funded by the industry, regulator–industry consultation was tolerated, drug approvals were rapid and plentiful, and senior managers in regulatory agencies had assimilated the interests of industry. Throughout the 1980s and early 1990s, the corporate bias of pharmaceutical regulation in the US converged with that of the European model in those respects. Thus, the US was 'catching up' with EU in adopting neo-liberal corporate bias as a regulatory reform programme. The second phase of convergence relates to the deregulatory reforms themselves

adopted by (or imposed on) the regulatory agency, such as accelerated approval rules, use of surrogate measures of clinical outcomes, and risk management strategies. All of those specific deregulatory reforms were introduced into the US first. By the late 1990s and 2000s, the supranational EU drug regulatory system was emulating the US by introducing new legislation and regulations, such as conditional marketing approval and the European Risk Management Strategy, as well as beginning to promote further use of surrogate biomarkers.

Our macro- and meso-level investigations in this chapter have identified specific key changes to regulatory standards for innovative pharmaceuticals resulting from neo-liberal reforms in the US and the EU. These include: the broadening of drug innovations that should receive priority review; the widening of the types of conditions for which drugs intended to treat them may attain 'accelerated approval' or 'conditional marketing'; the use of non-established surrogate markers of drug efficacy together with companies' post-marketing commitments to establish efficacy; and the implementation of risk management in response to safety problems emerging with innovative drugs after marketing.

Senior officials in both the pharmaceutical industry and regulatory agencies have continually insisted that such reforms have increased the efficiency of the drug development and review process without lowering drug review standards. That new drug review times have fallen in the EU and the US following neo-liberal reforms is undeniable but, as we have indicated, whether that has delivered more 'efficiency' is dramatically called into question by the fact that the reforms were also followed by declines in innovation and new drugs that offer therapeutic advance. Regarding the issue of whether standards of safety and efficacy to promote and protect public health have been compromised by specific deregulatory measures, this question cannot be fully addressed without a micro-level examination of the regulatory science surrounding innovative pharmaceutical products themselves. It is to that issue that we now turn for the remainder of this book, before drawing out our final overall conclusions.