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BALANCING SAFETY AND AVAILABILITY:
A HISTORICAL PERSPECTIVE ON THE PACE OF DRUG
APPROVAL, 1950s–2009.

A Thesis Submitted to the
Yale University School of Medicine
In Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Fabienne C. Meier-Abt

February 2009

Abstract. Over the course of the past 50 years, drug approval processes have ranged from 42 days to more than 10 years. What are the consequences of slow or rapid drug approvals on drug safety and drug availability? How slow is too slow? How fast is too fast? These questions have engaged the public, the government, physicians and the pharmaceutical industry for decades. This essay adopts a historical approach to examine the search for the right balance between drug safety and drug availability in the changing political climates of the past 60 years.

Before 1962, the discovery of life-saving antibiotics fostered an emphasis on drug availability and the rapid marketing of drugs. On the background of the thalidomide crisis in the early 1960s, however, the drug approval process was reframed. The 1962 Kefauver-Harris Amendments ensured a new focus on drug safety rather than drug availability. Efficacy standards were introduced and safety standards raised, and as a result drug approval and drug marketing times increased.

During the 1970s, the term ‘drug lag’ was coined and rapidly endorsed by pharmaceutical companies, physicians and by conservative parties. The term referred to the unnecessary suffering of American patients as a result of the delayed market introduction of life-saving drugs in the United States. On the background of general consumer movements and as illustrated by the case of sodium valproate, patients, too, used the notion of ‘drug lag’ as a political weapon to fight government regulations on the pharmaceutical industry.

In the context of the Reagan Administration’s emphasis on economic deregulation and of the public health crisis caused by the emergence of AIDS, the political pressure on the Food and Drug Administration rose, and the drug review process was revised to emphasize drug availability rather than drug safety. In the late 1980s and throughout the 1990s, several measures were introduced, intended to reduce drug approval and drug marketing times, especially for drugs targeting life-threatening diseases.

Finding the right balance between drug safety and drug availability has been a controversial task. As illustrated by the case of gefitinib, the current system depends very heavily on postmarketing studies and on trust in the pharmaceutical industry’s ethical behavior. So far, however, the drug industry has not proven to deserve such trust, as exemplified by cases like rofecoxib. Hence, in 2009, the drug approval process awaits to be reframed again. A renewed focus on drug safety with more careful pre-approval studies and more thorough drug reviews seems warranted.

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Balancing Safety and Availability: A Historical Perspective on the Pace of Drug Approval, 1950s–2009.

1.

Introduction

In June 2006, the Food and Drug Administration (FDA) approved the human papillomavirus (HPV) vaccine Gardasil for the prevention of cervical cancer related to HPV via a fast track process. Accelerated approval programs, as employed with Gardasil, had been introduced in 1992 and 1993 to provide rapid and widespread access to potentially life-saving drugs before the completion of large-scale and long-term clinical trials. Gardasil's approval for the target population of sexually naïve pre-adolescent girls rested on two studies measuring immune responses at four weeks after the last dose of vaccine.¹ The lack of extensive efficacy studies and long-term safety tests in girls aged 9-15 raised the question of whether the FDA's decision to accept Gardasil for accelerated approval was premature. Groups like the National Vaccine Information Center (NVIC), founded in 1982 by parents of vaccine injured children, argued, "there is too little long term safety and efficacy data, especially in young girls... to recommend Gardasil for universal use".² According to NVIC, nobody knew whether Gardasil would make some pre-adolescent girls more likely to develop inflammatory autoimmune disorders or other diseases as teenagers or adults. NVIC further pointed out that the manufacturer of Gardasil, the pharmaceutical firm Merck, had used potentially reactive aluminum containing placebo as a control for most trial participants, rather than non-reactive saline solution. Because a vaccine can appear safer when compared against a reactive placebo than when compared against a non-reactive control substance, the NVIC accused Merck of "flawed science" and concluded, "it was

¹ FDA. Clinical Review of Gardasil Trials. www.fda.gov/cber/products/gardasil.html, accessed 2006.

² Merck's Gardasil Vaccine Not Proven Safe for Little Girls; National Vaccine Information Center Criticizes FDA for Fast Tracking Licensure. *PR Newswire*, June 27 2006.

inappropriate for the FDA to fast track Gardasil”.³ For the United States, NVIC promoted the sole use of routine pap screening to prevent cervical cancer until more tests on Gardasil have been performed.

The NVIC was not alone in questioning the FDA’s drug review process with respect to Gardasil. Several scientists pointed to the short trial durations, which prevented definite conclusions on the incidence of cervical cancer with Gardasil use at the time of the vaccine’s approval in the United States.⁴ Whereas this observation primarily inferred a need for further long-term clinical trials, it also raised more far-ranging questions relating to the pace of the drug approval process in general. What are the consequences of slow or rapid drug approvals on drug safety and drug availability? Who is interested in rapid drug availability, potentially at the expense of drug safety and efficacy? Who is interested in high safety and efficacy standards, potentially at the expense of rapid drug availability? What is the right balance between these conflicting interests and between slow and fast drug approval processes? Over the course of the past 50 years, drug approval processes have ranged from 42 days to more than 10 years. How slow is too slow? How fast is too fast?

The following essay constitutes a case study in the field of drug regulations. It discusses the power struggle between the pharmaceutical industry, physician organizations, patients and the government on issues of public safety, drug efficacy, drug availability and drug innovation. Whereas the public has traditionally sided with the government in promoting its safety, this has not necessarily been the case with respect to drugs. For much of the past decades, the public favored fast access to drugs over extensive proofs of drug safety and efficacy. On the background of the changing role of government in the late 1960s and early 1970s and the economic

³ Merck’s Gardasil Vaccine Not Proven Safe for Little Girls; National Vaccine Information Center Criticizes FDA for Fast Tracking Licensure. *PR Newswire*, June 27 2006.

⁴ Hymel, P. 2006. Decreasing Risk: Impact of HPV Vaccination on Outcomes. *Am. J. Manag. Care.* 12:S473-S483.

deregulation climate in the 1980s and early 1990s, this essay examines the tension between drug safety and drug availability.

Thereby, the essay adopts a historical approach to analyze the tradeoffs between long drug approval processes striving for high standards of proof for drug safety and efficacy, and short drug approval procedures aiming at the rapid market availability of drugs. A wide selection of primary and secondary sources and two carefully chosen case studies serve to document the positions of the pharmaceutical industry, physician organizations, patients, the government, and the media. The essay uses primary sources from scientific journals, newspaper archives, and FDA regulatory documents.

Several authors have accessed this issue tangentially. The historian and journalist Philip Hilts, for example, argues in his book *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation* in favor of substantial governmental control over the pharmaceutical industry. He harshly criticizes any attempts at providing more rapid market access to new drugs at the expense of loosened standards of drug safety and efficacy. Fran Hawthorne, a senior editor of the financial publication *Institutional Investor*, takes an economic approach to examining the FDA and the American drug regulations. In her book *Inside the FDA: The Business and Politics behind the Drugs We Take and the Food We Eat*, she partially reinforces Hilts' conclusions by arguing for a strong position of the FDA. However, unlike Hilts, Hawthorne believes in a constructive together and a close collaboration of pharmaceutical companies, physicians, scientists, the FDA and the public. Arthur Daemrich, a policy analyst at the Chemical Heritage Foundation, goes even a step further than Hawthorne. In his book *Pharmacopolitics: Drug Regulations in the United States and Germany*, he compares the American system of drug regulations with the German system. He illustrates how different regulatory solutions are explored in different countries to solve similar problems. According to Daemrich, these specific solutions reflected the needs and national regulatory cultures of the

particular countries. Daemmrich concludes by arguing not only for the close collaboration of pharmaceutical companies, physicians, scientists, the government and the public within a country, but also across country borders, resulting in the “international harmonization”⁵ of drug regulation.

The present essay offers a detailed study of a particular aspect in the history of drug regulation in the United States. It argues that the balancing of drug safety, efficacy and availability was a major issue in regulatory reform. Thereby, the creation of the notion of a ‘drug lag’ was a powerful weapon in the debate.

The essay begins by describing the events which led to the drug regulatory changes in 1962. The 1962 changes to the U.S. drug regulations were a crucial point in the history of American drug marketing and its governmental control. For the first time, drug approval was rendered an active process requiring an acceptance letter from the FDA. Before 1962, prescription drugs were automatically considered approved, unless the FDA intervened within 60 days after the filing of a new drug application.

The marked power differential which existed before 1962 and favored the pharmaceutical industry over the FDA was reversed by the 1962 Kefauver-Harris Amendments to the U.S. drug regulations. After 1962, the power to set the manufacturing and marketing standards rested with the FDA and the government, whilst the burden to prove a drug safe and effective lay on the drug manufacturers. Concomitant with the shift in authority, the pace of drug approval processes and the balance between drug innovation, drug availability and drug safety, became a major focus of discussion amongst physicians, pharmaceutical firms and the government. Their opinions and interests clashed on numerous occasions.

One of these occasions was the approval of the drug sodium valproate in 1978. However, whereas the debate on drug regulations previously excluded the public and did not arouse

⁵ Daemmrich, A. 2004. *Pharmacopolitics: Drug Regulations in the United States and Germany*. Chapel Hill and London: The University of North Carolina Press, p. 161.

extensive media coverage, the case of sodium valproate provoked patients to speak up and became the focus of numerous newspaper articles. Hence, the case of sodium valproate is interesting not only as an illustration of the different interests of the groups mentioned above, but also as a manifestation of the 1970s consumer movement and the concurrent new criticism of medical practice, themselves rooted in the 1968 counterculture. For these reasons, the case of sodium valproate constitutes the first case study in this essay.

On the background of the Reagan Administration's emphasis on economic deregulation and the emergence of the AIDS crisis, the essay then examines the revision of the U.S. drug regulations in the late 1980s and early 1990s. The new regulations aimed to shorten the time required to bring new drugs onto the market. The essay discusses the effects of the revised drug regulations as perceived by patient organizations, physicians, pharmaceutical companies, the media, and the government.

In order to demonstrate the struggles of authority between the pharmaceutical industry, the government, physicians and patients in more recent years, the cancer drug gefitinib was chosen as a second case study. The case of gefitinib appeared ideal because it constituted a case of extremes with respect to all aspects involved: the drug intended to treat the extremely deadly disease of lung cancer, which not only was (and is) the number one cause of cancer death within the United States, but also was (and is) a disease with virtually no effective treatment alternatives. On the basis of gefitinib's approval in 2003 and the drug's "life" in medical practice until its market limitation in 2005, the essay illustrates conflicting interests, challenges and power struggles relating to drug approval processes at the beginning of the 21st century.

Finally, the essay concludes by discussing the relationship between the pace of drug approval processes and drug safety and drug availability. It examines the present arguments for and against an emphasis on drug safety or drug availability. Extrapolating from the observations of the past 50 years and considering recent cases like rofecoxib and current topics like genomics

and personalized medicine, the cost of medical treatment, controversies over embryonic stem cells and over “vanity drugs”, the essay explains why a reframing of the issue of drug approval seems warranted.

2. The 1962 Kefauver-Harris Amendments

Since 1938, the United States had a Federal Food, Drug, and Cosmetic Act that aimed to ensure the safety of marketed drugs. According to the 1938 Act, drug manufacturers had to conduct pre-clinical and clinical tests to prove a drug's safety. The FDA then had 60 days to review a drug application and file objections or ask questions. If the FDA did not request additional testing data or refused a drug's marketing within these 60 days, then the new drug was automatically considered approved.⁶

The case of the drug efocaine illustrates the process of drug marketing and the role of the FDA before 1962. The anesthetic efocaine was introduced to the market in 1952. The FDA had not intervened within its 60 day time period, thereby accepting a single small test on animals as sufficient for drug approval. Soon, however, the drug was found too toxic to be kept on the market. At least twenty-eight papers had appeared in the medical literature describing cases of severe side effects from efocaine. In response, the manufacturer decided to withdraw the drug from the market. Of note, all of this happened without the FDA's knowledge, which only held a single file comprising a case report on the drug.⁷

Some years later, after the initiation of investigations aimed at changing the position of the FDA, Hubert Humphrey, chairman of the senate subcommittee on reorganization, summarized his findings on the state of the FDA prior to 1962:

“The more we have examined the handling of drugs by the Food and Drug Administration, the more we have been surprised, shocked and disappointed ... Often

⁶ Federal Food, Drug, and Cosmetic Act of June 25 1938. §505.

⁷ Brittingham, T.E., Berlin, L.N., and Wolff, H.G. 1954. Nervous System Damage Following Paravertebral Block with Efocaine: Report of Three Cases. *J. Am. Med. Assoc.* 154(4):329-330. Clarke, E., Morrison, R., and Roberts, H. 1955. Spinal Cord Damage by Efocaine. *Lancet.* 268(6870):896-898. Parsonage, M.J., Taverner, D., and Wooler, G.H. 1955. Paraplegia Following the Use of Efocaine. *Br. Med. J.* 1(4925):1322-1323. Hiltz, P.J. 2003. *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation.* New York: Alfred A. Knopf, p. 162-163.

testing had been going on in a manner which should have sent shivers down the spine of the medical profession ... drugs intended for use by victims of chronic disease – day after day, year after year – were released by the FDA even before, I repeat *before* chronic toxicity tests had been completed on animals ... shocking reports of injuries and deaths to test patients, as received by drug companies, have gone unreported to the FDA, or have been downgraded by skillfully-contrived half-truths, or have been reported accurately to the FDA, but virtually ignored ... Drugs have been approved which the FDA now admits should never have been approved. Drugs have been kept on the market long after the FDA admits they should have been eliminated.”⁸

Of interest, it was not the occurrence of drug tragedies or the feeble state of the FDA prior to 1962 that started attempts to change the drug regulations in the late 1950s, but economic concerns regarding drug prices.

In the context of widespread concerns about inflation in the 1950s, the populist Democratic senator Estes Kefauver started to investigate several industry sectors, including the pharmaceutical industry, with respect to “administered prices” or prices fixed by industry leaders. Starting in 1959, consumer prices for prescription drugs were examined in senate hearings, which focused on the large difference between manufacturing costs and the final market price.⁹ According to Arthur Daemmrch, Kefauver “wanted to protect captive consumers and indigent patients from companies that colluded to set high drug prices”.¹⁰ In order to achieve this goal, Kefauver presented a bill in fall 1961, designed to increase competition among pharmaceutical companies. The bill also intended to increase the FDA’s authority to inspect and license manufacturers, and it introduced the requirement of drug efficacy for approval in addition to the

⁸ Hiltz, P.J. 2003. *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*. New York: Alfred A. Knopf, p. 163.

⁹ Senate Subcommittee on Antitrust and Monopoly. *Administered Prices*.

¹⁰ Daemmrch, A. 2004. *Pharmacopolitics: Drug Regulations in the United States and Germany*. Chapel Hill and London: The University of North Carolina Press, p. 13.

existing requirement of drug safety. Kefauver further argued for the federal enforcement of antitrust laws and the compulsory cross-licensing of drug patents. Especially these latter two provisions aroused intense opposition from the pharmaceutical industry and several influential senators. When Kefauver refused to accept revisions to his bill suggested by the Judiciary Committee, his bill seemed doomed to fail.¹¹

At this point, however, reports of birth defects related to the sedative thalidomide, appeared in the popular press, aroused public concern and induced Congress to have a second look at the Kefauver bill.¹² The use of thalidomide by pregnant women had led to the birth of children with congenital abnormalities ranging from stunted arms and legs, abnormal hands and feet, to damaged internal organs. Between 1959 and 1963, some 10,000 deformed children were born around the world and thousands had died from their deformities before birth.¹³ Approximately half of the thalidomide-damaged children were born in West Germany alone.¹⁴ Because the FDA had not approved thalidomide and had prevented the domestic marketing of the drug, only seventeen cases of deformed babies linked to thalidomide were counted in the United States. Nevertheless, a public scandal emerged when it became known that the U.S. drug manufacturer William S. Merrell, Inc. had legally distributed over two million thalidomide tablets to some 1,200 practicing physicians in the United States as part of the drug's testing procedure.¹⁵ Numerous articles were published, such as the journalist John Lear's in the popular *Saturday Review*, demanding greater government oversight of testing processes and protesting, "they

¹¹ Harris, R. 1964. *The Real Voice*. New York: Macmillan. Daemmrch, A. 2004. *Pharmacopolitics: Drug Regulations in the United States and Germany*. Chapel Hill and London: The University of North Carolina Press, p. 25.

¹² Kelsey, F. 1966. The Evolution of New Drug Legislation. *BMQ*. 17:72-81.

¹³ Patrias, K., Gordner, R.L., and Groft, S.C. *Thalidomide: Potential Benefits and Risks*. www.nlm.nih.gov/pubs/resources, accessed April 2002. Hiltz, P.J. 2003. *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*. New York: Alfred A. Knopf, p. 158.

¹⁴ Patrias, K., Gordner, R.L., and Groft, S.C. *Thalidomide: Potential Benefits and Risks*. www.nlm.nih.gov/pubs/resources, accessed April 2002.

¹⁵ Daemmrch, A. 2004. *Pharmacopolitics: Drug Regulations in the United States and Germany*. Chapel Hill and London: The University of North Carolina Press, p. 26. www.fda.gov/cder/about/history/, accessed October 2008.

[pharmaceutical firms] may begin using drugs on humans before safety has been established through animal test, and they have the privilege of keeping the patients in ignorance throughout, lest knowledge of the guinea pig status have some undesirable psychologic effect on the results of the experiment.”¹⁶

In the light of such widespread public concerns, the drug testing provisions from Kefauver’s bill, combined with the consumer protection legislation from a separate bill by Representative Oren Harris, received unanimous approval in both the House and Senate. In October 1962, President John F. Kennedy, who had been pressing for radical measures with respect to drug regulations¹⁷, signed the Kefauver-Harris Amendments to the Food and Drug Act into law. New approval requirements of multiple prolonged testing steps were introduced to raise the safety standards, and proof of drug efficacy was added to the approval criteria in addition to the existing criterion of drug safety. Furthermore, explicit FDA approval was now a prerequisite for drug marketing, and FDA permission was required for the distribution of drugs to patients in clinical trials. Unlike before, the FDA now had authority over every stage of drug testing from laboratory to clinic. The FDA set the standards for “Good Manufacturing Practice” and reinforced its norms by regular plant inspections.¹⁸ The new regulations required the pharmaceutical companies to adapt their pre-clinical and clinical testing practices. Drug manufacturers were expected to perform extensive animal studies, to initiate formal arrangements with physicians carrying out clinical trials, and to apply complex statistical evaluations to demonstrate drug safety and efficacy. To further increase patient protection, clinical investigations by law involved three phases: Phase I trials comprised drug dosage tests in a small number of healthy subjects and intended to prove the safety of the drug and identify the tolerable dose range. Phase II trials involved initial tests on a limited number of patients with the disease. They were designed to

¹⁶ Lear, J. The Unfinished Story of Thalidomide. *Saturday Review*, September 1 1962, 40-42.

¹⁷ Hiltz, P.J. 2003. *Protecting America's Health. The FDA, Business, and One Hundred Years of Regulation*. New York: Alfred A. Knopf, p. 158.

¹⁸ Federal Food, Drug, and Cosmetic Act, as amended. § 505 (d), 1962.

establish the efficacy and suitable dosage of the drug. Phase III trials constituted large scale controlled clinical trials within the target population. During Phase III trials, the drug was expected to demonstrate its potential safety and efficacy under the anticipated conditions of usage.¹⁹

The enactment of the Kefauver-Harris Amendments set off an avalanche of protests from the pharmaceutical industry and physician organizations such as the American Medical Association (AMA).²⁰ Over 300 written objections were filed, expressing concerns over inflexible drug testing protocols and excessive and unnecessary record keeping. Fears were raised that the new regulations might delay the marketing of new drugs and thereby deny life-saving measures to patients who needed them.²¹ Furthermore, drug manufacturers predicted a decrease in drug innovation in the United States as a consequence of the Amendments. They warned that American drug businesses would have to cut expansion plans and might have to move out of the United States, thereby weakening America's position as an economic force.²²

Illustrative of the pharmaceutical industry's viewpoint, Irwin Winter, Vice-President of the pharmaceutical company G.D. Searle and Co., charged in 1964, "the development of a new drug under today's conditions is a much slower and more expensive process".²³ He explained that the insistence on the submission of all data, including all laboratory reports, for any conclusion of a clinical investigation was a most demanding, time-consuming and expensive task. It resulted in drug applications of enormous size, frequently counting more than 80,000 sheets of paper. Winter further pointed out that an increase in the size of drug applications also meant an enormous

¹⁹ New Federal Regulations for the Control of New Drug Testing in Humans. *J. New Drugs*. 1962, 373-376. Daemrich, A. 2004. *Pharmacopolitics: Drug Regulations in the United States and Germany*. Chapel Hill and London: The University of North Carolina Press, p. 28. Levy, J. 1982. The FDA Maze. *Cutis*. 29:54-60.

²⁰ Neibel, O.J. 1963. Rules, Regulations and Research. *New Physician*. 12:A85-A87.

²¹ New Federal Regulations for the Control of New Drug Testing in Humans. *J. New Drugs*. 1962, 373-376.

²² Hiltz, P.J. 2003. *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*. New York: Alfred A. Knopf, p. 161.

²³ Winter, I. 1964. Problems in Drug Development as They Relate to the Pharmaceutical Industry. *J. New Drugs*. 40:306-311.

increase in the workload imposed on the FDA. Frequently, the FDA would take six months to view an application just to return it as “incomplete”. Winter complained that letters from the FDA used the term “more”, meaning more experiments and tests, “almost as if building a legal defense, not a scientific argument”.²⁴ Thereby, Winter indirectly referred to the problem of interpreting the words “adequate and well-controlled studies”, which were required under the Amendments but not strictly defined. It appears that the FDA and the pharmaceutical industry had different ideas about what “adequate” and “well-controlled” exactly meant.

Furthermore, Winter criticized that it was difficult to have independent investigators under the new regulations because of the tremendous amount of formalities now required. This problem was brought up also by many physicians and will be discussed from their perspective later. Together with the increased number of required clinical trials, these circumstances pressured many pharmaceutical firms into establishing their own hospital ward systems. Such undertakings were time-consuming, extremely costly, and, thus, posed a serious problem especially to smaller companies.²⁵ John Krantz, Professor of Pharmacology at the University of Maryland School of Medicine, confirmed this, “several presidents of smaller companies have told me personally that they have abandoned all research efforts in the field of new drugs”.²⁶ It appeared that small companies could not afford the type of research required under the new regulations. Whereas it might be expected that the resulting reduction in competition on the drug market was welcomed by the larger pharmaceutical companies, it seems that their own agonies with the Amendments more than offset their apparent new advantage over the smaller pharmaceutical firms. According to Krantz, the larger pharmaceutical companies were not able to develop and market nearly as many new drugs in the years immediately following the new regulations as they were prior to the passage of the Amendments. In 1966, Krantz predicted not only financial difficulties for the

²⁴ *Ibid.*

²⁵ *Ibid.*

²⁶ Krantz, JJ. 1966. New Drugs and the Kefauver-Harris Amendment. *J. New Drugs*. 6:77-79.

pharmaceutical industry, but also a marked decrease in total health progress for the years following the implementation of the Kefauver-Harris Amendments.²⁷

As important cause for the expected drop in American drug innovation, Krantz specified the “appalling” time lags in getting information from the FDA, which in turn increased the time span for a new drug to reach the market. According to Krantz, the FDA was unprepared and insufficiently qualified to assume its new responsibilities. He criticized, “FDA has wavered, procrastinated, and quaked with indecision on rulings which often they are unqualified to make, owing to the multifaceted areas of medical science and medical practice involved”.²⁸ Following Krantz’s reasoning, such lack in qualification and competence, together with the enormous increase in workload, led to the time lags at the FDA that would ultimately decrease drug innovation in the United States.

Krantz’s charge of the FDA’s incompetence with respect to the authority over the efficacy of drugs was shared by many American physicians. Theodore Klumpp, MD, President of Winthrop Laboratories and FDA alumnus, spoke in the name of American physicians when he accused the FDA of developing “awesome powers ... over matters falling within the area generally known as medical opinion”.²⁹ Klumpp felt that the new regulations substituted the judgment of the FDA for that of physicians, including clinical investigators. Klumpp viewed this development as very problematic. He reasoned that it took years to decades of widespread clinical experience to evaluate the relative merits of a drug. The FDA, Klumpp argued, did not have this experience or knowledge, yet it sought to become the arbiter of medical opinion in the matter of drug efficacy. In dismay, Klumpp demanded, “in the long run the physicians of this country must be the judges of a drug’s efficacy and of its safety”.³⁰ In Klumpp’s and many American

²⁷ *Ibid.*

²⁸ *Ibid.*

²⁹ Klumpp, T. 1963. Regulations Affecting Drug Research and Development: A Historical Perspective. *J. New Drugs*. 41:212-20.

³⁰ *Ibid.*

physicians' eyes, the new regulations meant a return "to the Dark Ages". Before the Amendments, "experienced" physicians had decided what was safe and what worked. As the historian and journalist Hiltz pointed out, before 1962, the final arbiter was an "expert", not a governmental institution and not empirical scientific evidence. The new regulations placed experts in the second place, behind the FDA and behind scientific evidence.³¹ Many physicians felt deprived of an authority, which they had held firmly in their hands for decades. Furthermore, physicians argued that the control over drug efficacy studies had been assigned to an institution which was incompetent to effectively deal with it. Just like the pharmaceutical industry, physicians feared this incompetence to cause increased drug review times, thereby decreasing innovation in drug development and precipitating a halt in medical progress.

Along the same lines, the executive director of the college of American pathologists, Oliver Neibel, pointed out that the average physician at the FDA received \$12,000-\$15,000 per year in 1963. These were the people who had to evaluate the results, opinions, and tests of top rate clinical pharmacologists and physicians who were engaged in drug investigations, tasks that called for great knowledge and talent. Neibel argued, "you can't buy that kind of talent for that kind of money".³² He thus demanded that the FDA's appropriation be increased "so it can hire competent people to make the evaluations they now are required to make". Neibel hoped that by providing the FDA with more money and a larger staff, "we won't have valuable products withheld from the market for months and years because FDA can't get around to evaluating the voluminous reports being required".³³

Neibel also expressed the fear of many American physician practitioners that the new regulations were going to drive them out of the clinical drug testing process. He explained how up until now, the third phase of clinical trials had taken place largely in the offices of practicing

³¹ Hiltz, P.J. 2003. *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*. New York: Alfred A. Knopf, p. 164-165.

³² Neibel, O.J. 1963. Rules, Regulations and Research. *New Physician*. 12:A85-A87.

³³ *Ibid.*

physicians. However, after the Kefauver-Harris Amendments, clinical investigators were required to complete an enormous amount of paper work that was incompatible with carrying out the duties of a practicing physician at the same time. Neibel pointed out, “all of this information has to be provided, all of these records have to be kept. Where and how can the busy practitioner have the time to participate in this kind of study and still treat the sick...?”³⁴ As noted above, the loss of practicing physicians as clinical investigators created pressure on pharmaceutical firms to establish their own hospital ward systems for clinical research. This was expensive, time-consuming and added to the delay in bringing new drugs to the market.

In many ways, American physicians were aligned with the pharmaceutical industry in opposing the FDA and the new regulations during the years immediately following the implementation of the Kefauver-Harris Amendments, despite for different reasons. Drug manufacturers feared a decrease in drug innovation as a result of the Amendments and concomitant decreases in their profits. Physicians dreaded a potential decrease in drug innovation because it could deprive their patients of life-saving measures. Furthermore, physicians resented the government in taking over what they considered part of their authority. Both groups were set to “fight them [FDA] every step of the way”.³⁵

The FDA stood in the center of the criticism outlined above. How did it react? As might be expected, the FDA did not turn a deaf ear to the accusations from the pharmaceutical industry and American physicians. In response to the charge of inadequately qualified personnel at the FDA making decisions that ought to be made by experienced physicians, FDA Commissioner George Larrick countered, “the average practicing physician skilled as he may be in making decisions with regard to individual drugs to be administered to individual patients, is not necessarily qualified to make broader decisions about permitting nationwide marketing of a

³⁴ *Ibid.*

³⁵ *Ibid.*

drug”.³⁶ According to Larrick, practicing physicians often failed to see “the broader picture”. He argued that neither the physician who had encountered a rare but serious reaction from a drug, nor the physician who had successfully used the same drug on a hundred patients was in a desirable position to make a good judgment about the drug’s safety and efficacy. Larrick further questioned whether busy physicians were capable of keeping abreast of all the new developments on the drug market. Even though Larrick himself did not do so, this thought can be extended to the previous paragraphs: if practicing physicians, according to their own accounts, did not have the time to fill out investigational reports, did they have the time to study the efficacy details of the drugs on the market? Larrick also pointed out that the FDA employed physicians and pharmacologists skilled in making individual decisions and gave them “the training needed to make recommendations involving the broader picture of the relative merits of a drug for all of society”.³⁷ Thereby, the FDA intended to create people who both had the knowledge of practicing physicians and pharmacologists as well as the ability to see the broader context. Hence, from the FDA’s perspective, the charge of its incompetence was invalid and, thus, could not cause a decrease in health progress.

The same was not true for the charge of increased workloads overwhelming the FDA. Larrick admitted that the workload which fell upon the FDA’s medical officers was “enormous”. Per working day, the FDA received on average four applications, each thousands of pages long. Larrick defended the FDA, “we have taken a number of concrete steps to improve our operating procedures”.³⁸ Thereby, he referred to the internal reorganization of the agency and the recent recruitments that the FDA had undergone. Whereas in 1953, the FDA had only two medical officers, and six full-time and four part-time medical officers in 1960, in 1964, the FDA counted 41 full-time and three part-time medical officers. Nevertheless, Larrick’s arguments can be

³⁶ Larrick, G. 1964. How the Food and Drug Administration Evaluates New Drug Applications. *J. New Drugs*. 21:63-74.

³⁷ *Ibid.*

³⁸ *Ibid.*

interpreted as an acknowledgment of the Amendments' and FDA's contribution to potential delays in the marketing of new drugs.

In defense of the new regulations, Larrick reasoned that the Kefauver-Harris Amendments merely reflected the growing needs of the American society, "our Nation would no more have accepted new drug safety provisions in 1906 than it would permit the abandonment of new drug effectiveness requirements in 1964".³⁹ According to Larrick, the public and its representatives in Congress and the Senate had assigned increased powers to the government and the FDA because they felt a need for more safety on the drug market. Furthermore, Larrick stressed that the FDA did not intend to cause unnecessary difficulties for the pharmaceutical industry or the practicing physicians of the United States, and that the purpose of the new regulations was to protect the public whilst imposing "only necessary restrictions on the conduct of investigational drug research".⁴⁰ Again, it appears that the pharmaceutical industry, American physicians and the FDA had different notions about the exact meaning of certain expressions used in the Amendments. In this case, the dispute centered around the interpretation of "necessary restrictions".

James Goddard, who followed Larrick as FDA commissioner in 1966, was explicitly aware of the new powers, which – at least according to Larrick – the public had granted the FDA. At the Pharmaceutical Manufacturer's Association meeting in 1962, he addressed the company executives in a new tone. Countering the pharmaceutical industry's accusations regarding the FDA's work, he expressed how "shocked" he was at the low quality of many investigational new drug applications, "the hand of the amateur is evident too often for my comfort. So-called research and so-called studies are submitted by the cartonful..." Goddard continued that he could not take such applications seriously and informed the executives of his instructions to the FDA

³⁹ *Ibid.*

⁴⁰ Larrick, G.P. 1962. Title 21 - Food and Drugs. Procedural and Interpretative Regulations; New Drugs for Investigational Use. *J. New Drugs*. 376-384.

medical officers to cancel “unprofessional investigational new drug applications” immediately. With new authority, the FDA Commissioner Goddard scolded the executives, “if the sponsoring company is imprudent enough to waste stockholder’s money on low quality work, then that company must bear the consequence of such waste”.⁴¹ He added that the FDA should not be expected to waste public money by reviewing such low quality work. Furthermore, Goddard accused the pharmaceutical industry of trying to deceive the FDA and threaten its members, “I have been shocked at clear attempts to slip something by us. I am deeply disturbed at the constant, direct, personal pressure some industry representatives have placed upon our people.”⁴² Goddard warned the executives that such actions by the pharmaceutical industry built up pressure for even tighter federal control of the drug industry. Demonstrative of the FDA’s newly gained powers, Goddard could now threaten the drug manufacturers, “I will be candid with you ... the pharmaceutical industry as you and I know it today may be altered significantly, altered beyond your present fear ...”⁴³ And indeed, according to the FDA homepage, “Go-Go” Goddard, as he was known to his staff, displayed much “regulatory enthusiasm” during his years as the commissioner of the FDA.⁴⁴ Thereby, the pharmaceutical industry was the main bearer of Goddard’s efforts. For example, in Goddard’s first year at the FDA, drug recalls grew by nearly 75%. Clearly, the power differential had changed, perhaps even reversed.

Patient voices and the media were comparatively quiescent immediately after the implementation of the Kefauver-Harris Amendments. Their main concern had been the thalidomide crisis, which was effectively dealt with by the new regulations. Furthermore, before the 1970s, patients were not perceived as a separate interest group, but were felt to be best represented by their physicians. According to Jerome Halperin of the Food and Drug Law Institute in Washington, D.C., “medicine was one of those things where the patient was very

⁴¹ Hiltz, P.J. 2003. *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*. New York: Alfred A. Knopf, p. 168.

⁴² *Ibid.*, p. 168.

⁴³ *Ibid.*, p. 168.

⁴⁴ www.fda.gov/oc/commissioners/goddard.html, accessed October 2008.

passive. The FDA for the most part focused on the intermediary, the physician.”⁴⁵ It wasn’t until the 1970s that patient organizations developed a voice on their own and started to focus on drug approval processes. They did so as part of general consumer movements, which had been fueled by the 1968 counterculture activism and resulted in widespread criticism of governmental institutions and regulations. The consumer groups formed in the early 1970s, including the Public Citizens advocacy organization, its Health Research Group, and the Center for Science in the Public Interest, were bold and focused on their goals. For the most part, they had small budgets and used more volunteers than paid workers, forcing them to center on very specific issues. In the case of the Public Citizens’ Health Research Group and the Center for Science in the Public Interest, the emphasis was laid on the FDA and its regulations.⁴⁶ The consumer movement pressurized governmental institutions to make their files public and allow American citizens access to government meetings. Hence, while 90% of FDA files were secret before 1969, during the 1970s, 90% of FDA files became open to the public, permitting patient organizations access to data on drug trials and adverse reactions and pharmacologic details of drugs.⁴⁷ Furthermore, FDA meetings with expert committees were now held in the open for the most part, giving patients the opportunity to attend and sometimes to contribute, even if not according to protocol. Concomitantly, the feminist movement in the early 1970s and the discussions on the introduction of the oral contraceptive pill had provoked public criticism of physicians and medical practices. Physicians were no longer viewed as “half-Gods in white”.⁴⁸ Their judgment was challenged by patients, who tried to gain more control over their own bodies. All these developments facilitated the formation of a separate voice by patient organizations. Patients started to declare their interests just as the pharmaceutical industry, physicians and the government did. Thereby,

⁴⁵ Hawthorne, F. 2005. *Inside the FDA: The Business and Politics Behind the Drugs We Take and the Food We Eat*. New Jersey: John Wiley & Sons, p. 197.

⁴⁶ Hiltz, P.J. 2003. *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*. New York: Alfred A. Knopf, p. 197.

⁴⁷ *Ibid.*, p. 196-197.

⁴⁸ Nelson Pill Hearings, 1970.

realizing that even the simplest information could have an enormous impact if broadcasted in newspapers, consumer groups, including patient organizations, used the media to make themselves heard.⁴⁹

⁴⁹ Hiltz, P.J. 2003. *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*. New York: Alfred A. Knopf, p. 199.

3. The Argument of ‘Drug Lag’

Starting in the early 1970s, the argument of a ‘drug lag’ in the United States, which prevented the rapid market introduction of potentially life-enhancing and life-saving treatments, began to stir up patient organizations and the media and revived the government opposition of the pharmaceutical industry and physicians. Even though the pharmaceutical industry and American physician organizations had described fear, predictions, and existing indications of delayed approvals of drugs and a drop in medical progress in the United States immediately after the enactment of the Amendments, the notion of a ‘drug lag’, referring to a relative delay in the introduction of new drugs in America compared to other countries, first became an overriding issue in 1972. As the conservative economist Sam Peltzman from the University of California presented his analysis of the 1962 Amendments, promoters of drug business-friendly policies and opponents of strict governmental regulations on drug industry endorsed the concept of a U.S. ‘drug lag’. Although Peltzman had focused on cost-benefit studies rather than drug approval rates, he implied the probable existence of a ‘drug lag’ in an article published in *Science* in 1973. In the article, Peltzman concluded, “the probable cost of delayed introduction of unusually effective drugs, an inevitable result of the added testing required to satisfy the amendments, exceed many fold a generous estimate of the value of improved drug safety that the amendments are likely to produce”.⁵⁰ By “the probable cost of delayed introduction of unusually effective drugs”, Peltzman described in economic terms what the *Chicago Tribune* later described as potentially life-saving drugs that were not yet available in the United States and left American patients “needlessly suffering”⁵¹, thereby increasing physician and hospital bills and decreasing the country’s work force. According to Peltzman, such delay in the marketing of drugs in the United States was a consequence of the 1962 Amendments and created more costs than a concomitant improvement in

⁵⁰ Peltzman, S., and Wiener, H. 1973. Approval of New Drugs. *Science*. 181:110-112.

⁵¹ Steinbrook, R. Testing New Medicines: A Bitter Pill. *Chicago Tribune*, July 28 1977.

drug safety and efficacy could ever make up for. Of note, however, Peltzman assumed the Amendments to only prevent rare, well-publicized drug tragedies. In his analysis, he did not account for mishaps of lesser amplitude, nor did he consider other benefits from increased standards of scientific testing prior to drug approval such as information for physicians on how and when to use a specific drug.⁵²

As evidence for the presence of a ‘drug lag’ and a resulting drop in drug innovation in the United States as a consequence of the 1962 Amendments, Peltzman compared the number of drugs approved before the new drug law and after: 315 in 1959 versus about 80 in 1966. These numbers appear drastic and convincing. However, as the journalist and historian Philip Hilts pointed out, the number of drugs produced by the pharmaceutical industry and approved by the FDA had begun to decrease already in the late 1950s, making a direct connection between decreased drug innovation and the Amendments questionable. Furthermore, in Europe where no equivalent new law had been passed, there was a similar drop in the introduction of new drugs to the market. Hilts offered two explanations for these findings. According to Hilts, many new drugs in the 1950s had been so-called “me-too” drugs, very similar to already approved drugs, and combination-of-ingredients drugs. In the 1960s, scientists realized that not all “me-too” and combination-of-ingredients drugs were equally effective or even equally safe. This caused drug companies to back away from such drugs, thereby decreasing the total number of new drug developments. Furthermore, Hilts as well as many drug company leaders in the 1950s described a decline of new drug productions in the 1960s as inevitable because the chief scientific discoveries of the late 1940s and early 1950s, which had allowed for high drug development rates in the 1950s, were mined out by the early 1960s.⁵³

⁵² Hilts, P.J. 2003. *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*. New York: Alfred A. Knopf, p. 192-193.

⁵³ *Ibid.*, p. 194.

At the forefront of individuals and groups promoting the idea of a ‘drug lag’ in the United States was William Wardell of the University of Rochester School of Medicine. In 1973, Wardell published a landmark paper in the scientific journal *Clinical Pharmacology and Therapeutics*, comparing the introduction of new therapeutic drugs in the United States and Great Britain. In an extensive and thorough analysis of drug approval times from 1962 to 1971, Wardell found that nearly four times as many drugs were exclusively available in Britain. For mutually available drugs, the overall British lead in approval was twice that of the United States during the same time period. Wardell concluded from these results, “at least in numerical terms, the United States has lagged considerably behind Britain in the introduction of new drugs”.⁵⁴ He further extrapolated, “over the past decade the United States has been slow to introduce and by the end of 1971 still lacked an appreciable number of therapeutically useful drugs that had been available abroad for some years”.⁵⁵ Thereby, Wardell’s inference is based on the assumption that the drugs, which had not been introduced in the United States, were therapeutically important. His analysis, however, provided no information on the usefulness of the drugs investigated. Wardell did point out, though, that despite the fact that his results might not have answered the question of the therapeutic implications of the differences between drug approvals in the United States and Britain, his results provided “the data on which such a study needs to be based”.⁵⁶

Wardell’s data was given further credibility and meaning beyond 1971 by an article on the drug industry that appeared in the *British Medical Journal* and which reported that “in 1976, 2.6 times as many new drugs were introduced in Britain as in the United States; the ratio was 2.5 for France and 3.6 for Germany. On average, each year the three European countries introduced 2.9 times as many drugs as the United States.”⁵⁷ Furthermore, a West German study in the late 1970s showed that while the United States remained the leading producer of new drugs, it ranked

⁵⁴ Wardell, W. 1973. Introduction of New Therapeutic Drugs in the United States and Great Britain: An International Comparison. *Clin. Pharmacol. Ther.* 14:773-790.

⁵⁵ *Ibid.*

⁵⁶ *Ibid.*

⁵⁷ Smith, T. 1980. Are the Drug-Regulatory Agencies Paper Villains? *Br. Med. J.* 281:1333-1335.

ninth of twelve countries surveyed in approving the new drugs. “Between 1961 and 1977, 23.4 percent of all new drugs were discovered in the United States, but only 8 percent were first introduced in this country.”⁵⁸

Sensing a topic of public interest, American newspapers quickly responded to such scientific studies by presenting the results to the American public.⁵⁹ In 1978, the popular magazine *Newsweek* reported that the average time taken for the approval of a new drug application in the United States had risen from 14 months in 1963 to 26 months in 1977.⁶⁰ In contrast, most European countries required between 8 and 13 months.⁶¹ In 1979, the newspaper *Chicago Tribune* published an international comparison of drug approval rates, which ranked U.S. drug approval rates from the 15th on the anti-arthritic drug endomethacin to the 106th on the anti-bacterial drug co-trimoxazole. The United States was ranked 40th in the approval of the anti-tuberculosis drug carpreomycin, 65th in the approval of the anti-allergy drug chromolyn sodium, and 32nd in the approval of the anti-cancer drug andreomycin.⁶²

As to the cause of the apparent lag in the introduction of new drugs, Wardell traced it – like Peltzman before him – to the FDA’s rigorous Investigational New Drug procedures that were part of the 1962 Kefauver-Harris Amendments, and the “increasing constraints on human experimentation in American hospitals and prisons”.⁶³ According to Wardell and further discussed in the first case report of this paper, foreign countries had fewer requirements in these areas, rendering the drug approval process a faster and more efficient process.⁶⁴

⁵⁸ Vogel, D. 1989. AIDS and the Politics of Drug Lag. *Public Interest*. 73-85.

⁵⁹ Clark, M., Hager, M., and Gosnell, M. 1978. How Bad the Drug Lag? *Newsweek*. 92:119-121. Vogel, D. 1989. AIDS and the Politics of Drug Lag. *Public Interest*. 73-85.

⁶⁰ Clark, M., Hager, M., and Gosnell, M. 1978. How Bad the Drug Lag? *Newsweek*. 92:119-121.

⁶¹ Smith, R. 1979. Air is Once Again Rent by Drug Lag Claims. *Science*. 205:283.

⁶² Key, J. Aspartame Locked Up in Classic Case of FDA Inaction. *Chicago Tribune*, October 7 1979.

⁶³ Steinbrook, R. Testing New Medicines: A Bitter Pill. *Chicago Tribune*, July 28 1977.

⁶⁴ *Ibid.*

The pharmaceutical industry also blamed the FDA for what they called “drug lag” and “decrease in American health progress”, thereby implying a negative impact of slower drug introduction rates in the United States on the well-being of American patients. However, unlike Peltzman and Wardell, the pharmaceutical industry saw the problem not only in the requirements for more tests and better documentation since the Amendments in 1962, but also in the FDA’s new authority to set the norms and oversee all investigations carried out by drug manufacturers. This is illustrated by the complaint of Milton Mendlowitz, a researcher at Pfizer Pharmaceuticals. When the FDA halted his investigations because of a protocol alteration involving the increase in the dosage of an experimental drug given to humans, Mendlowitz filed an official complaint, accusing the FDA of unconscionably delaying his research and “hampering our efforts to study the effects of this drug”.⁶⁵ He charged, “such restrictions on a clinical investigator are, in my opinion, most undesirable unless they can be supported by incontrovertible evidence”.⁶⁶ Furthermore, several researchers at pharmaceutical firms accused FDA officers such as Richard Dunham of deliberately criticizing drug applications without giving details as to what needed to be changed. According to the drug manufacturers, the FDA officers’ lack of good will further increased the already existing delays in the introduction of new drugs onto the market.⁶⁷ It appears that the pharmaceutical industry deeply resented the position, which the drug law of 1962 had assigned to drug manufacturers and which forced pharmaceutical companies to carry the burden of proof for a drug’s safety and efficacy whilst the government and the FDA set the standards.

The American government responded to the widespread criticism regarding the slow introduction of new drugs in the United States by performing several studies. Of note are especially two studies: the General Accounting Office (GAO) study and a study performed by the

⁶⁵ Hiltz, P.J. 2003. *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*. New York: Alfred A. Knopf, p. 187.

⁶⁶ *Ibid.*, p. 187.

⁶⁷ *Ibid.*, p. 188.

Department of Health, Education, and Welfare's (HEW) Review Panel. In early 1979, the GAO concluded from its 2 year study that regulators in the United States took longer than their European counterparts to approve new drugs.⁶⁸ Tracking fourteen therapeutically significant new drugs, the GAO found that all but one had been introduced in Europe before they were available in the United States. Thereby, the lag ranged from two months to thirteen years.⁶⁹ Furthermore, according to the GAO, the FDA regularly exceeded its statutory limit for review of a new drug (6 month) by as much as 14 extra months⁷⁰, causing the average FDA approval time to exceed the approval time of every other surveyed country except Sweden.⁷¹ As causes for the delayed introduction of new drugs in the United States the GAO report named (i) delays within the FDA, "FDA delays its reviews by changing reviewers in midstream, by failing to use a computerized information system, by writing vague guidelines, and by failing to provide feedback swiftly to interested companies"⁷², and (ii) the reluctance of manufacturers to seek approval in the United States. The latter appeared to be especially true for drugs with safety problems. Such drugs seem to have been held back from the United States by their manufacturers whilst they were offered for sale elsewhere.⁷³ This dubious appearing behavior makes it more difficult to draw conclusions from the GAO's data with respect to the notion of 'drug lag'.

Another comprehensive study of the FDA's new drug approval process was conducted by the Department of Health, Education, and Welfare's (HEW) Review Panel on New Drug Regulation between February 1975 and May 1977. In its study on FDA policies and practices, the panel evaluated the arguments connecting the 1962 Amendments, particularly the efficacy requirement, to a potential 'drug lag' in the United States. The panel, which consisted of three

⁶⁸ Smith, R. 1979. Air is Once Again Rent by Drug Lag Claims. *Science*. 205:283.

⁶⁹ Key, J. Aspartame Locked Up in Classic Case of FDA Inaction. *Chicago Tribune*, October 7 1979.

Vogel, D. 1989. AIDS and the Politics of Drug Lag. *Public Interest*. 73-85.

⁷⁰ Smith, R. 1979. Air is Once Again Rent by Drug Lag Claims. *Science*. 205:283.

⁷¹ Vogel, D. 1989. AIDS and the Politics of Drug Lag. *Public Interest*. 73-85.

⁷² Smith, R. 1979. Air is Once Again Rent by Drug Lag Claims. *Science*. 205:283.

⁷³ Hiltz, P.J. 2003. *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*. New York: Alfred A. Knopf, p. 191.

physicians, three lawyers, and one scientist, concluded, “there was insufficient evidence to demonstrate a drug lag attributable to the 1962 legislation”.⁷⁴ Furthermore, countering the charges outlined above at least partially, the panel testified, “the system of new drug regulation ... is fundamentally sound”.⁷⁵ Of course, the question remained of exactly how fundamental “fundamentally sound” was, since few people disputed the very existence of drug regulations. Most likely, the panel referred to FDA’s authority over drug efficacy studies in addition to its authority over drug safety.

Although the HEW review panel viewed the new drug regulations as adequate, it pointed out some marked deficiencies in the law, which required improvement. According to the panel, the FDA’s minimum postmarketing authority constituted such a weakness.⁷⁶ As explained in the clinical journal *Annals of Internal Medicine*, once the FDA had approved a drug, it only had the right to withdraw the drug completely from the market when there was “imminent” danger to the public. This clause implied a standard so strict that it had been used only once in seventeen years. The FDA lacked the power to adopt less drastic regulatory actions, such as limiting the distribution of a drug to certain settings, directing drug sponsors to conduct additional studies, ensuring that informed consent be obtained from those using a drug, or requiring that patients receive inserts describing a drug’s benefits and risks. This effectively forced the FDA to receive all data on a drug’s performance prior to approval, resulting in a relatively inefficient and slow system.⁷⁷ *Annals of Internal Medicine* quoted the former FDA Commissioner Alexander Schmidt, “drug approval is now pretty much an all or nothing event. ... Since approval is our “last chance”,

⁷⁴ Dorsen, N., and Miller, J. 1979. The Drug Regulation Process and the Challenge of Regulatory Reform. *Ann. Intern. Med.* 91:908-913.

⁷⁵ *Ibid.*

⁷⁶ *Ibid.*

⁷⁷ *Ibid.*

we properly now tend to want all data in hand to be absolutely certain of every detail before approving a drug ...”⁷⁸

The HEW Panel was not the only voice arguing for the basic validity of the 1962 Amendments. Sidney Wolfe of the Health Research Group organization, a division of the consumer advocacy group Public Citizen, for example, reasoned that ‘drug lag’ was a poor argument against the existing drug regulations, because it measured mostly unimportant drugs and did not account for unsafe and inefficient drugs that were approved elsewhere even though they should not have been. Thereby, Wolfe referred to the fact that up to 95% of new drugs reaching the market were “me-too” drugs, which did not provide therapeutic progress and did not need to be rushed onto the market.⁷⁹ Wolfe’s proposition of unsafe and inefficient drugs being inappropriately approved abroad is substantiated by Hilts’ finding that more drugs had to be withdrawn from the market in Britain for safety reasons than in America. Hilts pointed to a study, according to which 20 hazardous drugs were recalled in Britain while in the same period only 10 drugs were withdrawn for safety reasons in the United States.⁸⁰

Proponents of the Amendments claimed that Conservatives and critics of governmental regulations used the concept of ‘drug lag’ to declare the need for reduced governmental control of the pharmaceutical industry. As Hilts pointed out, not so long before, President Kennedy had coined the term “missile gap” to refer to America’s lag in nuclear warheads behind the Soviet Union. The term became a potent political weapon. Similarly, Hilts claimed, the term ‘drug lag’ took on almost mythic connotations.⁸¹

⁷⁸ Symposium on Principles and Techniques of Human Research and Therapeutics, Tulane University School of Medicine, New Orleans, Louisiana, November 5 1975.

⁷⁹ Hilts, P.J. 2003. *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*. New York: Alfred A. Knopf, p. 191.

⁸⁰ *Ibid.*, p. 191.

⁸¹ *Ibid.*, p. 192.

In the light of the Carter administration's anti-regulatory tendencies with respect to economic policies and despite the administration's otherwise highly participatory attitudes, the FDA and its drug approval policies increasingly became the target of criticism centering on the notion of a 'drug lag' in the United States. In a time of fierce economic competition between the United States and Japan, the 'drug lag' was presented as proof that the erroneous drug regulations passed in 1962 had damaged the ability of American pharmaceutical firms to compete on the international drug market. The President's biomedical research panel was probably the most frank in blaming the FDA and the 1962 Amendments for preventing innovation at pharmaceutical companies, "... there is a different kind of hazard to public health posed by the prolonged delays and great costs of developing new and potentially useful drugs which the FDA's own protective systems have imposed. In some respects the agency has become a formidable roadblock."⁸² Thereby, the President's panel, like Peltzman, Wardell, and the pharmaceutical industry, connected a relatively slow introduction of new drugs in the United States to a decrease in public health, assuming that the drugs, whose approval lagged behind other countries, were crucial to therapeutic progress.

By the mid 1970s, even the FDA itself had endorsed the notion of a 'drug lag'. However, the FDA did not see the root of the problem in its own actions, but in the legislations that it had to work with. In 1975, the FDA Commissioner Alexander Schmidt explained that whenever a controversial drug was approved, the FDA would be investigated by Congress. However, whenever such a drug was disapproved, no inquiry would be made. Schmidt interpreted this as "Congressional pressure for negative action".⁸³ He demanded that Congress be as willing to investigate charges of non-approval of a drug as it was to investigate the opposite kind of allegations. Schmidt claimed, "until perspective is brought to the legislative oversight function, the pressure from Congress for FDA to disapprove new drugs will continue to be felt, and could

⁸² Smith, T. 1980. Are the Drug-Regulatory Agencies Paper Villains? *Br. Med. J.* 281:1333-1335.

⁸³ Schmidt, A. 1975. The Drug Approval Process and the FDA. *Conn. Med.* 39:237-240.

be a major factor in health care in this country”.⁸⁴ Thereby, the FDA Commissioner not only admitted that the FDA was inherently inclined to disapprove a drug and that this could be to the disadvantage of the American public, but he also pointed out who was to blame for it: Congress.

The phrase of ‘drug lag’ in the United States was applied to “medications for problems ranging from asthma to heart attacks”.⁸⁵ In October 1978, the magazine *Newsweek* reported, “the drug lag ... had unnecessarily postponed – or blocked –the introduction of beclomethasone, a revolutionary asthma remedy, as well as nearly a dozen major heart drugs”.⁸⁶ The journal quoted the cardiologist Myrvin Ellestad, “it’s a national scandal that our patients [cardiac patients] are deprived of lifesaving drugs available elsewhere in the world”.⁸⁷ Furthermore, in a speech in 1980, and specifically referring to propranolol, a heart drug, and adriamycin, a cancer drug, Democratic Representative James Scheuer of New York, chairman of a House subcommittee on science and technology, charged, “the FDA is contributing to needless suffering and death for thousands because it is denying them life-saving and life-enhancing drugs that are available abroad far sooner than they are here”.⁸⁸

In the context of the Carter administration’s concerns regarding America’s economic competitiveness, the apparent drop in drug innovation in the United States was framed as proof for the need for decreased regulations on the pharmaceutical industry. The notion of ‘drug lag’ was used as a political tool to effectively argue against governmental control over the drug industry.

A prominent drug, which illustrates the notion of a ‘drug lag’ in the United States, as well as the emerging influence of patient voices on drug policy during the 1970s, is the anti-epileptic

⁸⁴ *Ibid.*

⁸⁵ Clark, M., Hager, M., and Gosnell, M. 1978. How Bad the Drug Lag? *Newsweek*. 92:119-121.

⁸⁶ *Ibid.*

⁸⁷ *Ibid.*

⁸⁸ Vogel, D. 1989. AIDS and the Politics of Drug Lag. *Public Interest*. 73-85.

sodium valproate. Furthermore, this drug case also addresses the question of the therapeutic implications of a potential 'drug lag' in the United States.

4. Sodium Valproate: Patient Voices

The anticonvulsant properties of sodium valproate were discovered in 1963. Four years after its discovery, the drug was licensed in France, five years later in Britain. By 1978, sodium valproate was approved in most countries in Europe, the Middle East, Africa, Australia, Japan and the Soviet Union.⁸⁹

In 1967, the French manufacturer of sodium valproate, Labaz, approached ten American drug companies in order to reach a license agreement over the anticonvulsant. Nine of the ten American drug companies declined, and it wasn't until December 1974 that Abbott Laboratories agreed to apply for drug approval in the United States. The journalist James Kilpatrick saw the reason for this mainly in the high costs of getting a drug approved in the United States. The "staggering costs of winning FDA approval for a new drug", he argued, prevented many companies from applying in the first place unless they could be sure that the drug would pay off later on.⁹⁰ The latter was questionable in the case of sodium valproate, the potential market of which was relatively small. J. Kiffen Penry, chief of the epilepsy branch at the National Institutes of Health in Bethesda, explained, "it's true that there are hundreds of thousands of people in the United States who could benefit from this drug, but compared with the market for drugs for hypertension or antibiotics, that's relatively few".⁹¹ In any case, after three more years, in September 1977, Abbot Laboratories supplied its new drug application to the FDA.

After the Kefauver-Harris Amendments of 1962, the FDA required at least two scientifically acceptable studies demonstrating drug efficacy in order to approve a new drug. Several studies had been performed in Europe. However, the European studies were uncontrolled,

⁸⁹ Lublin, J.S. Firm Asked to Seek Approval of Drug to Treat Epilepsy. *Wall Street Journal*, July 28 1977. Kilpatrick, J.J. Increased Hope for Epileptics. *The Hartford Courant*, August 4 1977.

⁹⁰ Kilpatrick, J.J. Good, Bad News for Epileptics. *The Hartford Courant*, February 22 1978.

⁹¹ Cohn, V. Despite its Advisors FDA Bars Approval of Drug for Epileptics. *The Washington Post*, February 21 1978.

multicenter cohort surveys designed to study the efficacy of sodium valproate and to examine its general safety in epileptic patients resistant to other therapies.⁹² Although randomized controlled trials were considered the gold standard of clinical testing also in Europe, there was no randomization and no explicit control group apart from the historical control implicit in the clinical entry criteria of drug-resistant epilepsy in the European sodium valproate trials. The European conductors of the studies on sodium valproate argued that it was unethical in a disease such as severe, drug-resistant epilepsy, to use placebo controls or even to randomly assign separate active control groups. The FDA, however, did not regard the data generated by such studies as capable of providing “substantial evidence” of drug efficacy.⁹³ William Wardell from the University of Rochester commented this, “there is little doubt among medical or scientific experts (including the FDA’s own advisory committees), however, that such data can satisfactorily demonstrate drug efficacy”.⁹⁴ Whilst it can be questioned whether the FDA’s standards for accepting clinical trials were scientifically and medically appropriate, this did not change the immediate position of Abbot Laboratories.

Knowing that the European studies on sodium valproate were highly unlikely to be accepted by the FDA, Abbot Laboratories recommended the so-called 1972 Suzuki study in Japan and a double-blinded study of seizure victims at the University of Virginia medical center known as the Penry-Dreifuss study. Whereas the former study fulfilled all FDA requirements, the latter study was rejected on the grounds of insufficient evidence for the drug’s efficacy, despite the unanimously recommended acceptance of the study by the national epilepsy foundation and the FDA’s Neurologic Drug Advisory Committee.⁹⁵ Penry from the NIH pointed out that it was “very

⁹² Wardell, W., Tsianco, M., Anavekar, S., and Davis, H. 1979. Postmarketing Surveillance of New Drugs: II. Case studies. *J. Clin. Pharmacol.* 19:169-184.

⁹³ *Ibid.*

⁹⁴ *Ibid.*

⁹⁵ Cohn, V. After Years of Delay, FDA Set to Approve Drug to Help Epileptics in U.S. *The Washington Post*, February 25 1978.

strange for FDA not to accept the results of one of its own advisory committees”.⁹⁶ The newspaper *Hartford Courant* described the rejection of the Penry-Dreifuss study as a “maddening display of bureaucratic expertise”. It claimed, “the FDA staff didn’t understand epilepsy, and didn’t know how to evaluate the data”.⁹⁷ The Penry-Dreifuss study had been started in August of 1976 in American academic centers in order to “help FDA by doing the studies which drug companies haven’t been doing”.⁹⁸ One year later, in August 1977, Dr. Penry and Dr. Dreifuss had sent their preliminary results to Abbott, which had immediately filed with the FDA. The FDA’s Neurologic Drug Advisory Committee accepted the results.⁹⁹ However, the FDA staff did not. Eli Goldensohn of Columbia University, chairman of a national epilepsy panel, explained the FDA’s action by its main concern of “keeping bad drugs out, not (letting) good drugs in”.¹⁰⁰ Until now, the FDA had suffered politically more when it approved an unjustifiably dangerous drug than when it didn’t approve a useful drug. Richard Crout, director of the FDA’s Bureau of Drugs, elucidated, “the primary pressure from Congress and the public is to make no errors in regard to safety”.¹⁰¹ Hilts, on the other hand, argued that the FDA staff had merely followed the law. He pointed to the conclusions of the Supreme Court on the drug regulations at the time. In *Weinberger versus Hyinson*, a landmark legal case with respect to drug law in 1973, the Supreme Court had declared, “clinical impressions of practicing physicians and poorly controlled experiments do not constitute an adequate basis for establishing efficacy ... the legislative history of the act indicates that the test was to be a rigorous one”.¹⁰²

⁹⁶ Cohn, V. Despite its Advisors FDA Bars Approval of Drug for Epileptics. *The Washington Post*, February 21 1978.

⁹⁷ Kilpatrick, J.J. Good, Bad News for Epileptics. *The Hartford Courant*, February 22 1978.

⁹⁸ Cohn, V. Despite its Advisors FDA Bars Approval of Drug for Epileptics. *The Washington Post*, February 21 1978.

⁹⁹ Kilpatrick, J.J. Good, Bad News for Epileptics. *The Hartford Courant*, February 22 1978.

¹⁰⁰ Steinbrook, R. Testing New Medicines: A Bitter Pill. *Chicago Tribune*, July 28 1977.

¹⁰¹ *Ibid.*

¹⁰² Hilts, P.J. 2003. *Protecting America's Health. The FDA, Business, and One Hundred Years of Regulation*. New York: Alfred A. Knopf, p. 186.

Whatever the reasons for the rejection of the Penry-Dreifuss study by the FDA, it was at this point that patient organizations stepped in, developing a strong voice on their own. In a press conference in Washington on February 9th 1978, an independent panel of experts assembled by the Epilepsy Foundation of America, an organization of patients and their families and friends, stated that “further delays (in the introduction of sodium valproate) would constitute callous negligence”. The panel urged the FDA for “immediate approval” of sodium valproate for general use.¹⁰³ In the following weeks, many patients and patients’ families advocated their cause in numerous newspaper articles in an attempt to attract public and political attention. In February 1978, *The Washington Post* quoted the mother of a child with epilepsy, whose seizures could only be controlled with sodium valproate, “Michael’s doctor told us that if the FDA didn’t approve the drug, he might be allowed to keep only two patients on it [as part of an investigational program]. He asked us how he was to decide which two to keep.”¹⁰⁴

Whilst the rejection of the Penry-Dreifuss study definitely caused epilepsy patients and their families to raise their voices, some patients and patients’ families afflicted by epilepsy had tried to arouse public awareness already as early as in summer of 1977. In July 1977, in a *Wall Street Journal* article, a patient’s father described his “fight” with the FDA whilst taking his daughter to England for treatment with sodium valproate, “I believe we have won the fight... We’ll probably have the drug 18 months before we would have otherwise.”¹⁰⁵ Thereby, the individual resolution of the domestic drug availability problem in seeking treatment abroad was by no means uncommon or restricted only to epilepsy patients in the late 1970s. In an article on the beta1-selective blocker metoprolol in March 1977, *The Wall Street Journal* reported, “thus Mrs. G.B.’s doctor is giving her the European drug illicitly. ‘We told her about the drug and now

¹⁰³ Cohn, V. Despite its Advisors FDA Bars Approval of Drug for Epileptics. *The Washington Post*, February 21 1978. Kilpatrick, J.J. Good, Bad News for Epileptics. *The Hartford Courant*, February 22 1978. Valproic acid approved. *Ann. Neurol.* 1978, 3:A35.

¹⁰⁴ Cohn, V. Despite its Advisors FDA Bars Approval of Drug for Epileptics. *The Washington Post*, February 21 1978.

¹⁰⁵ Lublin, J.S. Firm Asked to Seek Approval of Drug to Treat Epilepsy. *Wall Street Journal*, July 28 1977.

she has someone get it for her in Europe.’”¹⁰⁶ In addition to illustrating how patients started to take matters into their own hands, the above quotes also demonstrate that it was the FDA which was blamed for the apparent ‘drug lag’ and its consequences. As noted earlier, the FDA in turn had blamed Congress¹⁰⁷, but this had at large not been recognized by the public, possibly because it was easier for the public to concentrate their blame on a single and isolated institution like the FDA and possibly also because such a diversion of the blame did not appeal to the media, thereby preventing the dissemination of the information.

The media quickly caught onto the topic of a government institution such as the FDA depriving American citizens of a life-saving and life-enhancing drug, and published several rather dramatic articles on sodium valproate. In summer 1977, the *Chicago Tribune* focused on the unnecessary suffering of epilepsy patients in the United States. The newspaper quoted Richard Masland, neurology department chairman at Columbia University’s medical school and executive director of a Congressional study commission on epilepsy, who estimated that sodium valproate “could prevent a million otherwise untreatable seizures in the United States this year” and exclaimed, “it’s absolutely frustrating to realize that patients I look upon by now as personal friends are needlessly suffering”.¹⁰⁸ In February 1978, *The Washington Post* published an article on sodium valproate titled “After Years of Delay, FDA Set to Approve Drug to Help Epileptics in U.S.” The article reported that “a drug that could help as many as a million Americans with epilepsy will be approved by the Food and Drug Administration ..., after ... months or years of unjustified delay”.¹⁰⁹ At the same time, *The Hartford Courant* charged, “because of the super-timidity of the Food and Drug Administration, valuable new drugs regularly are delayed for months or years in reaching the market; and in the specific case of sodium valproate, a needless

¹⁰⁶ Bronson, G. A Case of Caution. Heart Patients in U.S. Find Vital New Drugs Not Approved for Sale. Federal Agency Has Passed Only One Beta-Blocker, Others Sold Outside US. *Wall Street Journal*, March 7 1977.

¹⁰⁷ Schmidt, A. 1975. The Drug Approval Process and the FDA. *Conn. Med.* 39:237-240.

¹⁰⁸ Steinbrook, R. Testing New Medicines: A Bitter Pill. *Chicago Tribune*, July 28 1977.

¹⁰⁹ Cohn, V. After Years of Delay, FDA Set to Approve Drug to Help Epileptics in U.S. *The Washington Post*, February 25 1978.

delay was the result not merely of timidity but of incompetence as well”.¹¹⁰ By accusing the FDA of incompetence, *The Hartford Courant* probably referred to the FDA’s interpretation of the Penry-Dreifuss study as inadequate despite the suggested acceptance of the study by the national epilepsy foundation and the FDA’s Neurologic Drug Advisory Committee. Thereby, *The Hartford Courant* didn’t stop at calling the FDA incompetent, but questioned the very existence of the FDA. The newspaper and one of its journalists, James Kilpatrick, the author of a political column titled ‘A Conservative View’ and a “staunch opponent of actual or perceived federal encroachments”¹¹¹, asked their readers to “prompt renewed soul-searching on the whole business of FDA’s power over new drugs”.¹¹² Kilpatrick expressed his opinion which included “to strip the FDA of authority to pronounce upon efficacy, and to leave that judgment to doctors, to patients, and to the marketplace at large”.¹¹³ Of note, James Kilpatrick and *The Hartford Courant* were not the only ones that called for a decrease in the FDA’s power. In an article on the delayed U.S. approval of the beta-blocker propranolol, the traditionally deregulatory financial newspaper *The Wall Street Journal* raised “a question, unthinkable a few years ago, about whether we should even have an FDA. So far as we know, no one has added up the numbers on the lives that would have been prolonged in the absence of regulatory delays caused by the agency. But we are becoming increasingly convinced that they would far outweigh the number of lives likely to be lost or damaged if the responsibility for safety were merely returned to the drug makers and doctors. It should be kept in mind that drug makers and doctors also have a vital interest in drug safety for their own protection.”¹¹⁴ In the article titled ‘100,000 Killed’, *The Wall Street Journal* directly linked the death of patients to the ‘drug lag’, which it blamed on the government’s FDA.

¹¹⁰ Kilpatrick, J.J. Good, Bad News for Epileptics. *The Hartford Courant*, February 22 1978.

¹¹¹ www.wikipedia.org, accessed October 2008.

¹¹² Kilpatrick, J.J. Good, Bad News for Epileptics. *The Hartford Courant*, February 22 1978.

¹¹³ *Ibid.*

¹¹⁴ 100,000 Killed. *Wall Street Journal*, November 2 1981.

Not surprisingly, such headlines stirred up public emotions¹¹⁵, making them a potent political weapon in the battle against governmental regulations.

The pharmaceutical industry was also frustrated about the U.S. delay in drug approvals, exemplified by sodium valproate, despite for different reasons. The drug manufacturer's aggravation with long drug approval times in part arose from a concomitant shortening of drug patent periods with the extension of the drug approval process. For example, if the time for testing and review took up 10 years, which was not uncommon, then the life of the patent was reduced from the standard 17 years to only 7 years. This, in turn, markedly reduced the time available for the manufacturer to earn money from the drug's marketing before the emergence of imitators reduced the profit from the drug to very little.¹¹⁶ Pharmaceutical companies thus fiercely opposed the FDA's tight control measurements, which increased the time for bringing a drug onto the market. Joseph Stetler, head of the Pharmaceutical Manufacturers Association (PMA) exclaimed, "we're jaundiced from dealing with the FDA". He added that he did not believe that they would ever get faster approval.¹¹⁷

In the light of such pressure, and after the submission of the results of a clinical trial by B. J. Wilder of the University of Florida by Abbott Laboratories, the FDA approved sodium valproate on February 28th 1978 for the treatment of petit mal epilepsy and for the adjunctive treatment of partial and multiple seizure types.¹¹⁸ As Eli Goldensohn of Columbia University pointed out, this phrase "takes in just about everything".¹¹⁹ So when the FDA finally approved sodium valproate, it did so as broadly as physicians and patients had barely dared to hope for.¹²⁰

¹¹⁵ Letters to the Editor. *Wall Street Journal*, November 1981.

¹¹⁶ Levy, J. 1982. The FDA Maze. *Cutis*. 29:54-60.

¹¹⁷ Greenberg, D. 1978. Washington Report. Drug Regulation Reform. *N. Engl. J. Med.* 298:979-980.

¹¹⁸ Valproic acid approved. *Ann. Neurol.* 1978, 3:A35. Label on Sodium Valproate. www.fda.gov, accessed October 2008.

¹¹⁹ Cohn, V. After Years of Delay, FDA Set to Approve Drug to Help Epileptics in U.S. *The Washington Post*, February 25 1978.

¹²⁰ *Ibid.*

The case of sodium valproate provided a favorable context for numerous Drug Regulation Reform Act Hearings in the U.S. Senate and Congress in the late 1970s and early 1980s, aimed to find measures which would shorten the approval process for drugs with new therapeutic potentials.¹²¹ The provisions discussed included the authorization of the FDA to approve potentially life-saving drugs with unique therapeutic benefits before the completion of the usual efficacy tests. Furthermore, several steps were debated to increase the FDA's authority over already approved drugs. One of the suggested steps proposed a 5-year period of postmarketing surveillance at the drug sponsor's expense if HEW deemed it useful or necessary. Intentions were mentioned to permit the FDA to restrict the distribution of a prescription drug within specified limits. Moreover, the FDA was to be permitted to require informed consent from patients using certain prescription drugs. The provisions also included the drop of the "imminent hazard" standard, suggesting instead that a drug be removed from the market if it presented an "unreasonable risk of illness or injury".¹²² Finally, one of the measures intended to allow the FDA to make data on an investigational drug public prior to the drug's approval. This prompted the pharmaceutical industry to respond with "extreme distaste and promises of unrelenting opposition" to the proposed Drug Regulation Reform Act.¹²³ A staff member of the Pharmaceutical Manufacturers Association explained this response, "maybe they [people that FDA shows data to] are not competitors when they look at the material, but what's to stop them from going to work for a competitor the next day?"¹²⁴

¹²¹ Agenda of Senate and Congress Hearings, ProQuest; www.fda.gov/cder/about/history, accessed October 2008.

¹²² Dorsen, N., and Miller, J. 1979. The Drug Regulation Process and the Challenge of Regulatory Reform. *Ann. Intern. Med.* 91:908-913.

¹²³ Greenberg, D. 1978. Washington Report. Drug Regulation Reform. *N. Engl. J. Med.* 298:979-980.

¹²⁴ *Ibid.*

The Senate's and Congress's task of reforming the drug law with respect to drug approval times did not get any easier when the FDA commissioner Jere Goyan declared in a press conference in 1980:

“Our society has become overmedicated. We have become too casual about the use of drugs ... Too many people are taking too many drugs without proper understanding of their potential harmful effects ... I'm a therapeutic nihilist. My philosophy is the fewer drugs people take, the better off they are.”¹²⁵

Such a philosophy was hard to reconcile with policies which aimed to facilitate the fast approval of drugs, providing patients access to even more drugs that were even riskier. Furthermore, in line with the 1970s movement, which introduced doubt and criticism of the medical profession, Goyan did not trust physicians to competently and reliably protect patients from harmful drugs. Goyan believed physicians to be inattentive, often giving the wrong drug at the wrong time in the wrong amount, without regard to cost. At a physicians' meeting, Goyan proclaimed, “I staunchly refuse to accept the notion that any physician, merely because he graduated from medical school and is currently a card-carrying member of his or her county medical society, is great, or good, or even tolerably competent. Too much of drug therapy has been atrociously irrational.”¹²⁶ Goyan was thus not inclined to return to physicians any of the authority which had been assigned to the FDA by the 1962 Amendments, further complicating the creation of new regulatory policies.

Opposing interests and relatively balanced power struggles in the late 1970s and early 1980s prevented the introduction of major changes in regulatory policies. Nevertheless, the FDA felt enough pressure to make some serious attempts to reduce the review time for new drug applications. In 1978, the FDA established a three-year goal of reducing the processing time for

¹²⁵ Hilts, P.J. 2003. *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*. New York: Alfred A. Knopf, p. 207. Hawthorne, F. 2005. *Inside the FDA: The Business and Politics Behind the Drugs We Take and the Food We Eat*. New Jersey: John Wiley & Sons, p. 296.

¹²⁶ Hilts, P.J. 2003. *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*. New York: Alfred A. Knopf, p. 207.

“important” drugs by 25% and for all other drugs by 15%. However, despite initial developments which suggested reductions in drug review times, by 1985, it was difficult to escape the conclusion that the FDA’s attempts clearly did not reduce approval times.¹²⁷ The state of affairs was not changed much by the passage of the Orphan Drug Act in 1983 or the Patent Term Restoration Act of 1984. The Orphan Drug Act provided special incentives to the pharmaceutical industry to develop and market drugs for rare diseases which would otherwise be non-profitable.¹²⁸ If fewer than 200,000 people nationwide were affected by a condition, i.e. for a disease with a prevalence of less than 200,000 patients or for an orphan indication, pharmaceutical companies were given increased commercial exclusivity, 50% tax credit for money spent on clinical studies, and clinical research grants from the FDA, when they attempted to develop a drug to treat the condition.¹²⁹ The Patent Term Restoration Act, also known as the Hatch-Waxman Act, was a reaction to the pharmaceutical industry’s concern of shortened patent periods with long drug review times. By allowing patent-life extension equal to half the clinical phase and the entire review phase (the sum of which could not exceed five years), the Act restored patent terms and intended to foster innovation in the pharmaceutical industry in conjunction with the 1980 Bayh-Dole Act. (The latter allowed federal agencies to patent discoveries and license these patents to industrial enterprises, thereby facilitating the transfer of technology from the government and universities to industry.¹³⁰) Furthermore, the Hatch-Waxman Act streamlined the FDA review process for generic drugs.¹³¹

¹²⁷ Spivey, R., Lasagna, L., and Trimble, A. 1985. New Drug Applications: How Long to Gain Approval? *Clin. Pharmacol. Ther.* 37:361-366.

¹²⁸ Vogel, D. 1989. AIDS and the Politics of Drug Lag. *Public Interest.* 73-85.
www.fda.gov/cder/about/history, accessed October 2008.

¹²⁹ Arno, P., Bonuck, K., and Davis, M. 1995. Rare Diseases, Drug Development, and AIDS: the Impact of the Orphan Drug Act. *Milbank Q.* 73:231-252. Reichert, J. 2003. Trends in Development and Approval Times for New Therapeutics in the United States. *Nat. Rev. Drug Discov.* 2:695-702.

¹³⁰ Reichert, J. 2003. Trends in Development and Approval Times for New Therapeutics in the United States. *Nat. Rev. Drug Discov.* 2:695-702.

¹³¹ Hunt, M. 2000. Prescription Drugs and Intellectual Property Protection: Finding the Right Balance Between Access and Innovation. *National Institute for Health Care Management Issue Brief.* www.fda.gov/cder/about/history, accessed October 2008.

5. AIDS and the Revision of the U.S. Drug Regulations in the late 1980s and early 1990s

Under the presidency of Ronald Reagan, in the general atmosphere of reduced government regulations on the economy and a laissez-faire philosophy with respect to economic policies, the political pressure on the FDA and its regulatory policies increased dramatically. On this background, a clearly visible crisis in American drug regulation was provoked by the emergence and spread of HIV-AIDS. According to the journal *Public Interest*, the combination of three facts made the politics surrounding the medical treatment of AIDS unique. First, AIDS was fatal. Second, there were no existing drugs to treat it. Third, AIDS patients and their families and friends were vocal, well-organized, and aroused widespread public sympathy.¹³² Within the gay community and their supporters, AIDS activists established a sophisticated network including groups like the New York Gay Men's Health Crisis, San Francisco's Project Inform, and chapters of the AIDS Coalition to Unleash Power (ACT-UP).¹³³ AIDS activists were often highly educated, highly politicized and able to raise large budgets of hundreds of thousands of dollars for their cause. They could mobilize not only AIDS patients but the entire gay community and knew how to argue with government representatives.¹³⁴ The influential AIDS activists group ACT-UP/New York, for example, described itself as "a diverse, non-partisan group of individuals united in anger and committed to direct action to end the AIDS crisis"¹³⁵ and was "devoted to political action"¹³⁶. All of the above added weight to the AIDS activists' protesting of slow drug approval times and their pleading for faster access to drugs.

Thereby, the AIDS patient organizations identified the FDA as their primary target. Larry Kramer, a founder of the Gay Men's Health Crisis group and a well-known author, charged,

¹³² Vogel, D. 1989. AIDS and the Politics of Drug Lag. *Public Interest*. 73-85.

¹³³ Epstein, S. 1996. *Impure Science: AIDS, Activism, and the Politics of Knowledge*. Berkeley: University of California Press.

¹³⁴ *Ibid.*

¹³⁵ www.actupny.org/, accessed February 2009.

¹³⁶ Crimp, D. 1990. *AIDS Demographics*. Bay Press.

“there is no question on the part of anyone fighting AIDS that the FDA consists of the single most incomprehensible bottleneck in American bureaucratic history – one that is actually prolonging the roll call of death”.¹³⁷ In October 1988, more than a thousand AIDS activists demonstrated in front of the FDA headquarters in Rockville, Maryland. Shouting “drugs into bodies” and “FDA, you’re killing me”, AIDS activists attempted to “seize control” of what some called the “Federal Death Administration”.¹³⁸ A handbook distributed by ACT-UP explained the AIDS activists’ position, “like corporations, [government bureaucracies] consider the data of lives as raw material and grist for a perpetual-motion paper mill. Human need, suffering and death count for very little when compared to the imperatives of orderly process and well-maintained policies.”¹³⁹ Thereby, AIDS activists referred to ethical dilemmas such as the one of giving AIDS patients placebos in clinical trials, knowing that these patients would die soon. Articles in the gay press publicized the fate of the “sacrificial lambs” in the AZT studies, sentenced to “death by placebo”.¹⁴⁰ One trial subject who had discovered he was in the placebo group exclaimed, “Fuck them. I didn’t agree to donate my body to science, if that is what they are doing, just sitting back doing nothing with me waiting until I get PCP [*Pneumocystis carinii* pneumonia] or something.”¹⁴¹ He informed a reporter from the gay press that he had secretly begun taking dextran sulfate, an unapproved drug available on the black market.¹⁴² Of note, this trial subject’s attempt to get treatment underground was by no means a single incident. According to Daemmrich, AIDS patients challenged the authority of the FDA by carrying out underground tests of new drugs, by threatening to sabotage NIH-sponsored trials through premature distribution of data or by ignoring trial protocols. As

¹³⁷ Kramer, L. The FDA's Callous Response to AIDS. *New York Times*, March 23 1987.

¹³⁸ Epstein, S. 1996. *Impure Science: AIDS, Activism, and the Politics of Knowledge*. Berkeley: University of California Press, p. 255.

¹³⁹ Eigo, et al. FDA Action Handbook, p. 17. Epstein, S. 1996. *Impure Science: AIDS, Activism, and the Politics of Knowledge*. Berkeley: University of California Press, p. 255.

¹⁴⁰ Kingston, T. Death by Placebo: The Sacrificial Lambs of Protocol 019. *Coming Up!* September 1988, 10-11. Epstein, S. 1996. *Impure Science: AIDS, Activism, and the Politics of Knowledge*. Berkeley: University of California Press, p. 214.

¹⁴¹ Epstein, S. 1996. *Impure Science: AIDS, Activism, and the Politics of Knowledge*. Berkeley: University of California Press, p. 214.

¹⁴² *Ibid.*, p. 214.

examples, Daemmrich points to participants in the 1986 trials of AZT who – like the trial subject above – also took dextran sulfate, imported from Japan through an underground “buyers’ club”, and to underground tests, which made drugs available to anyone who wanted them, such as the covert tests carried out on “Compound Q”.¹⁴³ Daemmrich argued that AIDS patients “considered participation in trials a means to obtain potentially life-saving drugs, rather than a voluntary contribution to the more abstract common good of furthering knowledge about experimental therapies”.¹⁴⁴ His conclusion is substantiated by the AIDS activist Kramer’s assertion that “AIDS sufferers, who have nothing to lose, are more than willing to be guinea pigs”.¹⁴⁵

Martin Delaney, executive director of the San Francisco-based Project Inform, viewed the practices of AIDS patients, including “frequent cheating, even bribery, to gain entry to studies; mixing of drugs by patients to share and dilute the risk of being on placebo; and rapid dropping out of patients who learn that they are on placebo” as a “direct result of forcing patients to use clinical studies as the only option for treatment”.¹⁴⁶ Delaney warned, “it will soon be impossible to conduct valid clinical AIDS research in the U.S.”.¹⁴⁷ He used such conclusions as arguments to reframe the very purpose of the FDA from an institution, which sought to protect the public from ineffective or dangerous therapies, to an establishment, which should be actively involved in promoting access to potentially life-saving drugs.¹⁴⁸

Delaney’s painting of what the FDA’s function should be resonated well with the American political culture at the time, which was conservative and right wing. In a general move

¹⁴³ Daemmrich, A. 2004. *Pharmacopolitics: Drug Regulations in the United States and Germany*. Chapel Hill and London: The University of North Carolina Press.

¹⁴⁴ *Ibid.*, p. 97.

¹⁴⁵ Epstein, S. 1996. *Impure Science: AIDS, Activism, and the Politics of Knowledge*. Berkeley: University of California Press, p. 222.

¹⁴⁶ Delaney, M. 1989. The Case for Patient Access to Experimental Therapy. *J. Infect. Dis.* 159:416-419.

¹⁴⁷ Epstein, S. 1996. *Impure Science: AIDS, Activism, and the Politics of Knowledge*. Berkeley: University of California Press, p. 228.

¹⁴⁸ *Ibid.*

¹⁴⁸ Epstein, S. 1996. *Impure Science: AIDS, Activism, and the Politics of Knowledge*. Berkeley: University of California Press, p. 222.

of deregulation, the White House and conservatives throughout the country sought to reduce the FDA's control over the pharmaceutical industry, allowing for the faster marketing of new drugs. The right wing politicians hoped that such action would increase American drug innovation and thereby raise U.S. competitiveness on the international market. Recognizing their common interests, AIDS activists started to collaborate with conservative policy groups such as the Heritage Foundation and the Competitive Policy Institute. Alliances were formed that a few years earlier would have seemed upside down and most unlikely.¹⁴⁹

The gay community and AIDS patients felt in line with the Presidential Commission on the Human Immunodeficiency Virus, whose chairman, Admiral James D. Watkins, charged, "we don't have a system to move drugs rapidly into clinical trials".¹⁵⁰ Watkins predicted that "the FDA is going to be in very serious trouble very soon", unless the drug approval process were changed. He thus suggested that the FDA receive more financial and staff resources to handle the new applications and that it eliminate placebo drug trials for AIDS patients, arguing that giving placebos to victims of AIDS was immoral.¹⁵¹

The pharmaceutical industry, too, supported the Presidential Commission's suggestions. The vice-president of the Pharmaceutical Manufacturer's Association explained, "Admiral Watkins is calling for more resources to speed the approval of AIDS drugs that coincidentally would speed the approval process of all drugs. We certainly agree with that."¹⁵²

While the FDA started to work on a response to the unified demands of AIDS patient organizations, the White House, and the pharmaceutical industry, California acted on its own: It passed a new legislation that required the state's Department of Health Services rather than the FDA to handle applications for experimental AIDS drugs. Although most Californian

¹⁴⁹ *Ibid.*, p. 223.

¹⁵⁰ Vogel, D. 1989. AIDS and the Politics of Drug Lag. *Public Interest*. 77.

¹⁵¹ *Ibid.*, p. 77.

¹⁵² *Ibid.*, p. 77.

pharmaceutical firms were unable to take advantage of the new state law, California's decision had considerable national political impact by forcing Congress to reexamine the FDA's policies.¹⁵³

As a result of the pressures exerted on the FDA by the White House, Congress, the pharmaceutical industry and patient organizations, the FDA implemented a series of five initiatives, over the course of six years, designed to expedite the availability of drugs for seriously ill patients. The first initiative, known as the Treatment Investigational New Drug (IND) Regulation, was enacted in June 1987. The program made "promising investigational new drugs" available to patients for treatment purposes whilst additional data on the drug's safety and effectiveness was obtained. It only applied to drugs used for the treatment of "immediately life-threatening" and "serious" diseases for which no adequate therapy existed. The drug in question was required to be investigated in controlled clinical trials unless all clinical trials had been completed already. Furthermore, even though the manufacturing company was allowed to bill patients for the drug, the amount charged was not to exceed the manufacturing, research and development, and distribution costs.¹⁵⁴

In October 1988, the second initiative was enacted, the Subpart E Procedures. This regulation was designed to move drugs for life-threatening and serious illnesses rapidly and efficiently through the review phases onto the market. Subpart E allowed for a lot of flexibility in the evaluation procedures of the FDA. It required close collaboration between the drug manufacturer and the FDA from the early preclinical phase until the postmarketing surveillance. Efficiency and greater speed in the review process were achieved with ongoing clinical trial

¹⁵³ *Ibid.*, p. 73-85.

¹⁵⁴ 21 C.F.R. §312.34. Shulman, S., and Brown, J. 1995. The Food and Drug Administration's Early Access and Fast-Track Approval Initiatives: How Have They Worked? *Food Drug Law J.* 50:503-531.

monitoring and evaluation by the FDA, consideration of treatment IND status at the end of phase II trials, and the elimination of phase III clinical trials.¹⁵⁵

The revisions implemented in 1992 and 1993 were part of President George H. W. Bush's attempt to reduce the regulatory burden on industry.¹⁵⁶ They included the Parallel Track Policy, the Prescription Drug User Fee Act, and the Accelerated Approval Regulation.

The third initiative known as the Parallel Track Policy was established in April 1992 in order to expand the availability of "promising investigational therapies" beyond the parameters of the treatment IND regulations. The parallel track initiative allowed access to an investigational drug as early as the end of phase I trials, provided that phase II controlled clinical trials had been approved by the FDA. The policy was designed for patients with AIDS and HIV-related conditions, and was intended for patients who were unable or unwilling to take part in ongoing clinical trials. The program required participating physicians to file regular safety reports. Even though pharmaceutical companies were allowed to charge for drugs distributed under the parallel track program, they were to do so only after authorization from the FDA and prices were not to exceed mere cost-recovery.¹⁵⁷

The fourth initiative or the Prescription Drug User Fee Act of 1992 was a system that allowed the FDA to charge companies for the drug review process, in exchange for tighter adherence to deadlines.¹⁵⁸ It was created with the consent of the pharmaceutical industry and provided a rich source of income for the FDA, which used the money to increase staff and other

¹⁵⁵ *Ibid.*

¹⁵⁶ Gladwell, M. FDA Implements Changes In Drug Approval Process. *The Washington Post*, April 10 1992.

¹⁵⁷ 21 C.F.R. §312.7. Shulman, S., and Brown, J. 1995. The Food and Drug Administration's Early Access and Fast-Track Approval Initiatives: How Have They Worked? *Food Drug Law J.* 50:503-531.

¹⁵⁸ Daemmrich, A. 2004. *Pharmacopolitics: Drug Regulations in the United States and Germany*. Chapel Hill and London: The University of North Carolina Press.

resources to get the applications handled more quickly.¹⁵⁹ Furthermore, the Act contained five-year performance goals for the FDA, including the total elimination of the agency's backlog of overdue applications and the review of 90% of all new drug applications within 6 months for priority applications and within 12 months for standard applications.¹⁶⁰

The last and most radical initiative was implemented in January 1993. The so-called Accelerated Approval Regulation permitted the approval of a drug on the basis of its effect on a surrogate endpoint, which had to be reasonably likely to predict clinical outcome. Of note, no direct, validated link between the surrogate marker and clinical outcome was required at the time of approval. Examples of such surrogate markers comprised the CD4 cell count and P24 antigen levels with AIDS therapies. Thereby, several conditions could be attached to a drug's approval under the accelerated approval program, including the initiation and timely completion of phase IV studies (post-approval studies). The FDA could restrict the distribution and use of the drug in question to specific hospitals or groups of physicians. It was also allowed to require specific tests prior to drug administration. Furthermore, the FDA could request the withdrawal of the drug from the market if the anticipated favorable outcome failed to be confirmed in post-approval studies, if no appropriate post-approval studies were conducted, if the restrictions on distribution and use were violated or were deemed insufficient, or if there was evidence that the drug was unsafe or not effective.¹⁶¹

¹⁵⁹ James, J. 1996. FDA Reform in Congress: FDA's Concerns. Food and Drug Administration. *AIDS Treat. News.* 5-7.

¹⁶⁰ Kaitin, K. 1997. The Prescription Drug User Fee Act of 1992 and the New Drug Development Process. *Am. J. Ther.* 4:167-172.

¹⁶¹ 21 C.F.R. §§314.520, 601.42, §§314.550, 601.45, §§314.530, 601.43. Shulman, S., and Brown, J. 1995. The Food and Drug Administration's Early Access and Fast-Track Approval Initiatives: How Have They Worked? *Food Drug Law J.* 50:503-531.

6. Perspectives on the Revised Drug Regulations

The pharmaceutical industry, political conservatives, and many patient organizations and community physicians welcomed the FDA reforms, claiming that legislative action was necessary to speed the rate at which new medical products reached the marketplace. Critical voices, however, feared a reduction of FDA oversight and an increase in public exposures to potentially unsafe and/or ineffective drugs as a consequence of the reforms.¹⁶²

The pharmaceutical industry not only fully approved of the new regulations, but even advocated for more radical measures to shorten drug approval times. Drug manufacturers expected substantial financial profits from shorter review times and the early marketing of drugs. In the mid 1990s, industry representatives like Sam Kazman, General Counsel for the Competitive Enterprise Institute in Washington DC, asked for further fundamental reform of the FDA guidelines. More specifically, Kazman suggested that the FDA be made a “certification” agency rather than a “veto” agency. Thereby, Kazman referred to a system in which a drug could be put on the market and sold as a non-certified drug after it had passed basic safety requirements equivalent to phase I trials. Kazman argued that those physicians and patients who only wanted FDA-certified drugs could simply not buy the drug. This system would give every physician and patient a choice, giving each person the individual freedom that the American society believed in, according to Kazman. Sam Kazman further stressed that “drug safety is not a hard and fast concept. At the scientific level, it is often the subject of intense disputes among experts. At the level of personal values and decisions, therapeutic risks that are acceptable to one person may be out of the questions for another.”¹⁶³

¹⁶² Kaitin, K., and Manocchia, M. 1997. The New Drug Approvals of 1993, 1994, and 1995: Trends in Drug Development. *Am. J. Ther.* 4:46-54.

¹⁶³ Anderson, W. 1995. FDA Reform: Arguments on Both Sides. *Hum. Gene Ther.* 275-276.

Illustrative of the opinion of many business-friendly politicians, Louis W. Sullivan, physician, businessman, and Secretary of the U.S. Department of Health and Human Services under President George H. W. Bush, praised in 1992, “these actions will save both lives and money. They will substantially improve FDA’s ability to respond vigorously to the nation’s health needs by allowing important new drugs to be approved months or even years earlier than was previously possible.”¹⁶⁴

Unlike the pharmaceutical industry and political conservatives, the AIDS patient community was split in its views on the revised drug regulations. The Treatment Action Group (TAG), many members of which held important positions in politically powerful AIDS organizations, argued that the FDA reforms had gone too far. They called for a slowing in the drug approval process and more extensive drug testing before approval.¹⁶⁵ They were concerned about “inappropriately low standards”¹⁶⁶, “inadequate” clinical testing and about the “virtual absence of data” on newly approved drugs.¹⁶⁷ Representing Gay Men’s Health Crisis, Derek Link addressed the FDA in 1994 over the fast-track approval of an AIDS drug known as d4T, “you may be able to construct a case for approval, but there’s no way to look at the data and tell doctors how to use this drug”.¹⁶⁸ TAG member and AIDS activist Spencer Cox criticized, “you’ve got drug companies doing these teeny-weeny trials that will never tell us if the drug delays diseases and death ... I don’t know whether this drug would be helping me or would kill me faster”.¹⁶⁹ Cox explained further, “we pay huge amounts of money and we suffer through major toxicities, and we have to take the drug company’s word for it that these treatments work. They’re not doing

¹⁶⁴ Gladwell, M. FDA Implements Changes In Drug Approval Process. *The Washington Post*, April 10 1992.

¹⁶⁵ FDA Evaluates Accelerated Approval Process. Food and Drug Administration. *Common Factor*. 1995, 18. James, J. 1995. FDA Reform: Activists’ Proposals. Food and Drug Administration. *AIDS Treat. News*. 6-8.

¹⁶⁶ The Other Drug War. *The New Republic*, October 17 1994.

¹⁶⁷ Wyatt, E.A. Rushing to Judgment. *Barron’s*, August 15 1994.

¹⁶⁸ *Ibid.*

¹⁶⁹ *Ibid.*

me any favors by approving these drugs.”¹⁷⁰ Thereby, Link and Cox referred to the ability of experimental drugs to gain approval under the new regulations even if they had been tested only on a very small patient population. Moreover, the required trials did not determine whether a drug actually extended an AIDS patient’s life or eased the patient’s symptoms. Instead, the tests relied on surrogate markers for indication of a drug’s efficacy. AIDS activists like Derek Link and Spencer Cox questioned whether a specific surrogate marker such as the CD4 count could demonstrate a beneficial outcome, an issue which was also hotly debated by many physicians and scientists. David Feigel, director of the FDA’s division of antiviral drug products, admitted that even the FDA’s own antiviral advisory panel “clearly expressed concern about surrogate markers”.¹⁷¹ Thereby, those concerns were not limited to the mere question of which surrogate marker to use, but went as far as doubting the validity of surrogate endpoints in general. According to Feigel, “some members don’t believe surrogate markers should ever be used for anything”.¹⁷² However, whereas clinical trials with endpoints of life-extension and symptom-reduction often took years, clinical trials monitoring surrogate markers could be completed within months, which corresponded better with the goal of accelerated drug marketing.

In the mid 1990s, AIDS activists like Link and Cox, in conjunction with several physicians and scientists, argued that the rushed testing of experimental drugs under the new regulations prevented the acquisition of detailed information on the drugs’ side effects and efficacies. Link charged, “the kind of data that have come out of these clinical studies is uninterpretable and ambiguous. No one knows when to take them [drugs], how best to use them, or if the toxicities outweigh the benefit.”¹⁷³ Concomitantly, members of the FDA’s Antiviral Drugs Advisory Committee and the National Task Force on AIDS Drug Development urged that

¹⁷⁰ The Other Drug War. *The New Republic*, October 17 1994.

¹⁷¹ Wyatt, E.A. Rushing to Judgment. *Barron's*, August 15 1994.

¹⁷² *Ibid.*

¹⁷³ *Ibid.*

scientific standards be not sacrificed to political pressures.¹⁷⁴ In 1995, the National Minor AIDS Council (NMAC) warned from underrating the need to protect individuals, “NMAC’s priorities are to preserve the necessary regulatory elements that would protect consumers”.¹⁷⁵ Donald Abrams, assistant director of the AIDS activities division at San Francisco General Hospital, doubted that the clinical studies as performed for accelerated approval provided any significant information, “I’m not sure we’re advancing our knowledge at all”. He further questioned the right of patients to receive drugs prior to the completion of extensive clinical studies, “I don’t think it’s established in this country that people have a right to health care, so why should they have a right to investigational drugs?”¹⁷⁶ Joseph L. Fleiss, an FDA consultant and professor of biostatistics at Columbia University’s School of Public Health was one of the scientists that opposed the reforms on the grounds outlined above. He expressed himself rather bluntly in the financial magazine *Barron’s*, “I think the accelerated approval process is a horror. The person who thought of it and saw to its acceptance should be shot.”¹⁷⁷

Furthermore, AIDS activists like Link and Cox, physicians and scientists accused the FDA of not forcing drug companies to do adequate follow-up tests, or phase IV clinical trials, on drugs which had been granted accelerated approval. When confronted with this criticism, FDA’s Feigel conceded that the agency had not focused on pressing companies to do the required post-approval studies.¹⁷⁸ Furthermore, Whaijen Soo, the director of virology at the pharmaceutical company Hoffmann-La Roche, one of the large firms involved in producing AIDS drugs, admitted in 1994 that the company had abandoned some of its originally planned phase IV trials. However, he assured that these tests would be replaced by other ones that were to start soon.¹⁷⁹ To Ellen Cooper, a former director of the division of antiviral drugs at the FDA and director of

¹⁷⁴ Wyatt, E.A. Still on the Fast Track. *Barron’s*, September 19 1994.

¹⁷⁵ Agosto, M. 1995. FDA Reform. Food and Drug Administration. *Update Natl. Minor AIDS Counc.* 10.

¹⁷⁶ Wyatt, E.A. Still on the Fast Track. *Barron’s*, September 19 1994.

¹⁷⁷ Wyatt, E.A. Rushing to Judgment. *Barron’s*, August 15 1994.

¹⁷⁸ *Ibid.*

¹⁷⁹ *Ibid.*

clinical research and information at the American Foundation for AIDS Research at the time of the FDA reforms, the delay in phase IV trials was no surprise. She explained in a *New York Times* article in 1994 that once a drug was on the market, companies felt less compelled to conduct expensive studies which could, at best, confirm efficacy, but risked showing the drug not to work or to have unexpected side effects.¹⁸⁰ In addition, it might be speculated that many patients disliked being enrolled in postmarketing trials. If patients believed a newly approved drug superior to other treatments, they might prefer buying the new drug over being randomized into groups, only one of which would actually receive the new drug. This would not only add to the delay in phase IV trials, but, according to the FDA's Antiviral Drugs Advisory Committee, it would also underscore a "two-tier health care system" which forced poor and uninjured people to serve as research subjects.¹⁸¹

In addition to fears of delays in postmarketing studies, critical voices of the revised drug regulations, including many scientists, questioned whether the FDA would withdraw a drug if the efficacy standard was not met within a certain time frame after accelerated approval. In 1994, Paul Meier, professor of statistics at Columbia University, asked, "what about the situation where a drug has achieved some popularity on the market? If a drug is well-hyped and selling well, there's the potential to keep studies rolling and rolling."¹⁸²

David Barr from Gay Men's Health Crisis raised another point against the new regulations. What is good for an individual, he argued, may not be good for the patient community. Barr found it very understandable for a dying AIDS patient to want access to a potentially life-extending or life-saving new drug as quickly as possible, even if little data on the drug's safety and efficacy were present. However, if this meant that no extensive studies would be performed to determine the drug's characteristics or such studies would only be performed with

¹⁸⁰ Kolata, G. FDA Debate on Speedy Access to AIDS Drugs Is Reopening. *New York Times*, September 12 1994.

¹⁸¹ Antiviral Drugs Advisory Committee, Meeting #22, p. 368-69

¹⁸² Wyatt, E.A. Still on the Fast Track. *Barron's*, September 19 1994.

much delay, then, Barr reasoned, the debate became one in part about altruism. Barr would rather have good information on a drug for future patients than he would have a drug without data on if, how, and when it should be used for individual patients right now. “It’s not just me who has to take the drugs, not just a group of informed people, but doctors and patients all over the world need to know what works. And this is not just for today. In five years there’ll be a whole lot more people looking for treatment options and trying to figure out what to do, what works. Part of what we’re doing is not just for ourselves, but is, unfortunately, planning for them also.”¹⁸³ Many scientists argued along similar lines. They feared that the new procedures would not provide them with all the information they needed to direct their research and identify and potentially resolve the problems, which might otherwise harm millions of patients in the future.¹⁸⁴ Scientist and health official Ellen Cooper viewed it as a simple question of the greatest good for the greatest number. According to Cooper, the individual’s right to treatment had to take a back seat to research which could benefit the public at large.¹⁸⁵ Thereby, Cooper acknowledged the emotional difficulty of the situation, stressing how much she understood and empathized with the individual patient with a life-threatening disease.¹⁸⁶

Food and Drug Commissioner David A. Kessler responded to the criticism raised against the new regulations in the mid 1990s, “we stand firmly behind the idea of accelerated approval for life-threatening and serious diseases”.¹⁸⁷ He argued that by changing “the rules of the game”, the FDA was “trying to be more flexible and trying to meet patients’ needs”.¹⁸⁸ Moreover, Kessel

¹⁸³ Brown, D. Speedy Release of AIDS Drugs Challenged on Lack of Follow-Through. *The Washington Post*, September 11 1994.

¹⁸⁴ Evaluating AIDS Drugs. *The Washington Post*, September 15 1994.

¹⁸⁵ Boffey, P.M. Washington Talk: FDA: At Fulcrum of Conflict, Regulator of AIDS Drugs. *New York Times*, August 19 1988. Epstein, S. 1996. *Impure Science: AIDS, Activism, and the Politics of Knowledge*. Berkeley: University of California Press, p. 227.

¹⁸⁶ Epstein, S. 1996. *Impure Science: AIDS, Activism, and the Politics of Knowledge*. Berkeley: University of California Press, p. 227.

¹⁸⁷ Brown, D. Speedy Release of AIDS Drugs Challenged on Lack of Follow-Through. *The Washington Post*, September 11 1994. Wyatt, E.A. Still on the Fast Track. *Barron's*, September 19 1994.

¹⁸⁸ Wyatt, E.A. Still on the Fast Track. *Barron's*, September 19 1994.

pointed out, “the issue here is not whether we will make a mistake”¹⁸⁹, thereby acknowledging and accepting the increased risk to patients who received drugs after accelerated approval. Nevertheless, he admitted that the accelerated approval process could use “fine-tuning”, especially in finding ways to ensure the completion of follow-up studies on approved new drugs.¹⁹⁰ Otherwise, Kessel reasoned, physicians and patients might not get the information they needed to use the new drugs.¹⁹¹ Furthermore, Kessel guaranteed that the threat of withdrawal of a drug was a real one in the absence of proof of efficacy after accelerated approval. He admitted, however, “we [the FDA] can do a better job of having our expectations understood”.¹⁹²

In line with the revised drug regulations and even asking for more aggressive changes, were AIDS activists like Martin Delaney, the director of Project Inform, an advocacy group in San Francisco. Delaney argued that proposals like TAG’s were a step backward and added, “people are not willing to go backward on the question of access”.¹⁹³ Similarly, Thomas Merrigan, the director of the center for AIDS Research at Stanford University, spoke in favor of the new regulations, “a long time ago, I felt like you had to see through the complete development of a drug before you released it, now I think that, for AIDS, you need early release”.¹⁹⁴ Delaney was very influential in constructing a consensus statement¹⁹⁵, which reflected the wishes of several AIDS organizations in 1995, many of which were situated on the West Coast and included groups like the San Francisco AIDS Foundation, the National AIDS Treatment Advocacy Project, ACT-UP/Golden State.¹⁹⁶ The consensus statement outlined suggestions to the FDA of how new

¹⁸⁹ *Ibid.*

¹⁹⁰ *Ibid.*

¹⁹¹ Brown, D. Speedy Release of AIDS Drugs Challenged on Lack of Follow-Through. *The Washington Post*, September 11 1994.

¹⁹² Wyatt, E.A. Still on the Fast Track. *Barron's*, September 19 1994.

¹⁹³ Kolata, G. FDA Debate on Speedy Access to AIDS Drugs Is Reopening. *New York Times*, September 12 1994.

¹⁹⁴ *Ibid.*

¹⁹⁵ James, J. 1995. FDA Reform: Activists' Proposals. Food and Drug Administration. *AIDS Treat. News*. 6-8.

¹⁹⁶ Baker, R., Delaney, M., Getty, J., Grinberg, L., and Levin, J. 1995. Policy Statement on FDA Reform. Food and Drug Administration. *BETA*. 45-46.

treatments could be brought to patients even faster without dismantling the overall system. The suggestions included the proposal that the FDA should “routinely encourage not only parallel track programs after phase I has been completed..., but also emergency access for individuals even before the completion of phase I”.¹⁹⁷ Furthermore, according to the statement, the FDA’s current program of accelerated approval “can be improved by resolving several bottlenecks”.¹⁹⁸ The statement continued by listing these “bottlenecks”, giving potential resolutions, and by making three more general suggestions such as the right for drug developers to appeal FDA decisions.¹⁹⁹

In response to the charge of missing data on drugs approved via the accelerated pathway, ACT-UP activist Mark Harrington argued that the primary aim was treatment, not research, thereby justifying the collection of little data. Furthermore, he expressed his concern, shared by his group ACT-UP and other AIDS activists, of a delay in innovative treatment processes if physicians were overwhelmed with the paperwork required for extensive data collection. Rather than attempting to assemble more data, the FDA should work on further accelerating the process of making new drugs available to dying patients.²⁰⁰

FDA Commissioner David Kessler replied to such requests by warning, “if you rush too much, you’re either going to do something potentially dangerous or turn down applications and take longer in the end”. On this point, Kessler for once had the sympathy of one of the most prominent FDA critics, Louis Lasagna, dean of the Sackler School of Graduate Biomedical Sciences at Tufts University. Lasagna admitted that the FDA could be “tempted to cut corners” to meet tight deadlines on reviews, a most undesirable effect.²⁰¹

¹⁹⁷ James, J. 1995. FDA Reform: Activists' Proposals. Food and Drug Administration. *AIDS Treat. News*. 6-8.

¹⁹⁸ *Ibid.*

¹⁹⁹ *Ibid.*

²⁰⁰ Skerrett, P. 1990. Parallel Track: Where Should It Intersect Science? *Science*. 250:1505-1506.

²⁰¹ Kaiser, J. 1996. FDA Reform Starts Down the Track. *Science*. 271:1228.

Given all these expectations, concerns and fears in the mid 1990s with respect to the new FDA regulations, the question arises of what the actual effects of the reforms were on drug approval times. The case of indinavir or Crixivan, a HIV protease inhibitor, illustrates what was possible after the enactment of the new initiatives: The drug was approved in 1996 under the accelerated approval regulation in a record time of only 42 days.²⁰² Thereby, the approval was based on two controlled clinical trials which used the surrogate markers of viral load and CD4 cell count as evidence of indinavir's efficacy.²⁰³

In a paper in the *American Journal of Therapeutics*, Kenneth Kaitin and Michael Manocchia analyzed the overall effects of the new FDA regulations on the amount of time required for drug approvals. For the 1993-1995 new chemical entity approvals, they found a mean approval time which was 21% faster than that for the 1990-1992 approvals and 29% faster than the average approval time from 1987 to 1989. Thereby, the total phase for accelerated approval drugs was 36% shorter than the value for all new drug entities. Furthermore, the percentage of approved new drug entities first available in the United States had risen to 32% (from 8% in the 1970s²⁰⁴). Kaitin and Manocchia concluded that their data offered encouraging evidence of faster new drug application approval times and rapid access to drugs intended to treat life-threatening and severe diseases.²⁰⁵

Moreover, a report from the Government Accounting Office (GAO) in 2002 found a median decrease in approval times for standard drugs – those that provided no significant therapeutic benefit over drugs already on the market – from about 27 months in 1993 to about 14 months in 2001. During the same period, according to the GAO, the median approval time for priority drugs – those intended to provide therapeutic benefits beyond drugs already on the market

²⁰² Hiltz, P.J. With Record Speed, FDA Approves a New AIDS Drug. *New York Times*, March 15 1996.

²⁰³ Daemrich, A. 2004. *Pharmacopolitics: Drug Regulations in the United States and Germany*. Chapel Hill and London: The University of North Carolina Press.

²⁰⁴ Vogel, D. 1989. AIDS and the Politics of Drug Lag. *Public Interest*. 73-85.

²⁰⁵ Kaitin, K., and Manocchia, M. 1997. The New Drug Approvals of 1993, 1994, and 1995: Trends in Drug Development. *Am. J. Ther.* 4:46-54.

– decreased from about 33 months in 1987 to 21 months in 1993 to around six months in 1997, at which point it remained stable.²⁰⁶ Already in an earlier report, the GAO had concluded that the FDA had met its performance goals for 1997 three years ahead of schedule.²⁰⁷ FDA Commissioner David Kessler, pleased with these results, attributed the agency’s success in reducing new drug review times mainly to the Prescription Drug User Fee Act (PDUFA) of 1992.²⁰⁸ In an independent study at the Tufts Center for the Study of Drug Development, Kenneth Kaitin showed the PDUFA to have indeed resulted in a “notable improvement” in FDA drug review times.²⁰⁹ The importance of the Act for the FDA was also demonstrated by the GAO, whose analysis showed that by 2002 industry provided about half the funds for all drug reviews.²¹⁰

Of interest, the GAO also reported a slight increase in drug withdrawal rates since the new regulations had been enacted, from 3.1% for 1985-92 to almost 3.5% for 1993-2000.²¹¹ At first sight, these numbers appear low. However, if one considers that at least 95% of all new drugs were so-called “me-too” drugs²¹², almost identical to drugs already on the market and of little or no additional therapeutic benefit, then a withdrawal rate of 3.5% does not seem so low anymore. (According to the National Institute for Health Care Management, 60% of new drug applications approved by the FDA in 1990-1999 were for drugs containing already existing active ingredients, and 50% of drugs approved during that time period were either new formulations or new

²⁰⁶ GAO Report 2002. James, J. 1996. FDA Reform in Congress: FDA’s Concerns. Food and Drug Administration. *AIDS Treat. News.* 5-7. Hileman, B. 2002. Side Effects from FDA’s Drug User Fees. *Chem. Eng. News.* 80.

²⁰⁷ James, J. 1996. FDA Reform in Congress: FDA’s Concerns. Food and Drug Administration. *AIDS Treat. News.* 5-7.

²⁰⁸ James, J. 1996. FDA Reform in Congress: FDA’s Concerns. Food and Drug Administration. *AIDS Treat. News.* 5-7. Kaitin, K. 1997. The Prescription Drug User Fee Act of 1992 and the New Drug Development Process. *Am. J. Ther.* 4:167-172.

²⁰⁹ Kaitin, K. 1997. The Prescription Drug User Fee Act of 1992 and the New Drug Development Process. *Am. J. Ther.* 4:167-172.

²¹⁰ Hileman, B. 2002. FDA Walks a Fine Line. *Chem. Eng. News.* 58-65.

²¹¹ GAO Report 2002. Hileman, B. 2002. Side Effects from FDA’s Drug User Fees. *Chem. Eng. News.* 80.

²¹² Hilts, P.J. 2003. *Protecting America’s Health: The FDA, Business, and One Hundred Years of Regulation.* New York: Alfred A. Knopf.

combinations of drugs already on the market.²¹³) Similarly, the interpretation of the reported increase in drug withdrawal rates is not straightforward. The observed increase could be attributed to a loss in drug safety as a result of the FDA reforms. Alternatively, the higher consumption of drugs by the U.S. population in the 1990s could have made adverse side effects more likely to be detected, and the increase in drug withdrawal rates merely showed that the FDA had taken rapid action. The FDA endorsed the latter explanation, adding that higher drug consumption rates also made the misprescription of drugs more likely, which was another reason for withdrawal.²¹⁴ The pharmaceutical industry, on the other hand, simply denied the existence of an increase in drug withdrawal rates since 1993. Jeff Trewhitt, a spokesman for the Pharmaceutical Research & Manufacturers of America, reported that from 1971 to 1992 the drug withdrawal rate for safety reasons was 2.5 to 3% and that it had been stable since then.²¹⁵

In addition to demonstrating a decrease in the approval time of new drugs, the studies outlined above noted a concomitant increase in the time required for research and development. The net result of shortened FDA review times and longer clinical development times was an only marginally shortened total time from the start of clinical testing to drug approval.²¹⁶ A possible explanation of these findings may lie in the FDA's actions to ensure high quality applications from the start: If applications showed severe deficiencies, the FDA refused to file them.²¹⁷ However, as Kaitin and also Peter Barton Hutt, expert on regulatory law at Harvard Law School, pointed out, there were numerous reasons for an increase in drug research and development times

²¹³ Hunt, M. 2000. Prescription Drugs and Intellectual Property Protection: Finding the Right Balance Between Access and Innovation. *National Institute for Health Care Management Issue Brief*.

²¹⁴ Hileman, B. 2002. Side Effects from FDA's Drug User Fees. *Chem. Eng. News*. 80.

²¹⁵ *Ibid.*

²¹⁶ Kaitin, K. 1997. The Prescription Drug User Fee Act of 1992 and the New Drug Development Process. *Am. J. Ther.* 4:167-172. Kaitin, K., and Manocchia, M. 1997. The New Drug Approvals of 1993, 1994, and 1995: Trends in Drug Development. *Am. J. Ther.* 4:46-54.

²¹⁷ Hileman, B. 2002. Side Effects from FDA's Drug User Fees. *Chem. Eng. News*. 80.

during the 1990s, many of which are still poorly understood.²¹⁸ An extensive discussion of those reasons is beyond the scope of this essay, but some suggestions and ideas are provided in the conclusion.

With the resolution of the problem of ‘drug lag’, a new set of concerns arose, ranging from the feared effects of decreased safety and efficacy standards to a dreaded lack in scientific information. An additional point of concern was raised by the FDA Commissioner David Kessler in 1996, “we can speed up the process but that doesn’t mean everyone will have access to these drugs because not everyone will be able to afford them”.²¹⁹ Furthermore and critical especially for the case of indinavir or Crixivan, limited supplies and limited manufacturing capabilities by Merck Pharmaceuticals prevented early wide public access to this life-saving drug.²²⁰ Whereas the latter issue could be resolved by building new factories to increase production²²¹, the former issue remains to be a problem in the United States and will be discussed briefly later on.

To date, there have been no more major changes in the U.S. drug law with the exception of the 1997 FDA Modernization Act (FDAMA). The latter intended to encourage the domestic transmission of new technology and enable pharmaceutical firms to reduce clinical study time. It also provided the FDA with a “fast track authority” to process applications for priority drugs even quicker.²²² According to a study performed by the National Institute for Health Care Management, the implementation of FDAMA decreased the average number of years for clinical drug investigations from 6.8 years in 1990-1992 to 5.9 years in 1996-1998. Combined with the shorter FDA approval times secondary to the regulatory reforms of the early 1990s, FDAMA

²¹⁸ Kaitin, K. 1997. The Prescription Drug User Fee Act of 1992 and the New Drug Development Process. *Am. J. Ther.* 4:167-172. Hutt, P. 1996. FDA Reform in Congress: Interview with Peter Barton Hutt. Food and Drug Administration. Interview by John S. James. *AIDS Treat. News.* 4-5.

²¹⁹ McGinley, L. FDA to Quickly Clear Merck AIDS Drug, after Approving Abbott's Treatment. *Wall Street Journal*, March 4 1996.

²²⁰ Daemmrich, A. 2004. *Pharmacopolitics: Drug Regulations in the United States and Germany*. Chapel Hill and London: The University of North Carolina Press.

²²¹ *Ibid.*

²²² Hunt, M. 2000. Prescription Drugs and Intellectual Property Protection: Finding the Right Balance Between Access and Innovation. *National Institute for Health Care Management Issue Brief*.

caused a reduction in total drug developmental times of about 2.1 years from 1993 to 1999. For pharmaceutical companies, this meant a gain in effective patent life, and high profits from a drug, of 2.1 years on average.²²³ Furthermore, a process commonly known as Single-Patient Investigational New Drug Application or Compassionate Use Program, designed to give individual patients with serious conditions access to drugs as early as Phase II clinical trials, allowed community physicians in 2000 to take on the responsibility of clinical investigators.²²⁴ The ability of local physicians to treat patients with non-approved investigational drugs returned to physicians an area of expertise and authority, which they had lost almost 40 years earlier after the 1962 Amendments (see above).

²²³ *Ibid.*

²²⁴ Morehead, J. 2002. Single-Patient Access to Investigational Drugs: Friend or Foe? *Biotechnology Law Report*. Daemmrich, A. 2004. *Pharmacopolitics: Drug Regulations in the United States and Germany*. Chapel Hill and London: The University of North Carolina Press.

7. Gefitinib: Recent Arguments

In recent years, several specific drug cases have again poured fuel into the debate about the U.S. drug regulations. One of these cases is the approval and subsequent market limitation of the cancer drug gefitinib or Iressa. Gefitinib was developed by the pharmaceutical company AstraZeneca to specifically target and inhibit the epidermal growth factor receptor (EGFR), a tyrosine kinase receptor which is implicated in a number of tumors. AstraZeneca focused on the use of gefitinib in “non-small cell lung cancer” (NSCLC) with the plan to extend the drug’s use later to other kinds of cancer. Lung cancer is the leading cause of cancer deaths in the United States. It comprises small cell lung cancer and a number of other entities, which are commonly referred to as non-small cell lung cancer. NSCLCs are notorious for responding very poorly to conventional chemotherapy. Hence, a stage III or IV NSCLC, i.e. a tumor which is not amenable to surgical resection, carried a very poor prognosis with a very low 5-year life-expectancy before the development of targeted therapies, of which gefitinib was the first agent.

When lung cancer patients heard about the development of gefitinib and the results of a small, uncontrolled clinical trial, which had shown significant tumor shrinkage by gefitinib as a third-line treatment in 10.6% of patients, they lobbied aggressively for rapid access to the drug.²²⁵ Cancer patient organizations approached AstraZeneca to hand out gefitinib as part of their drug investigations, and they appealed to the FDA to accept gefitinib for accelerated approval.²²⁶ The patients were joined by the pharmaceutical industry and financial organizations in their demands for quicker access to gefitinib. AstraZeneca’s Chief Executive Sir Tom McKillop argued that the rapid approval of gefitinib would offer “further hope” to patients suffering from a “devastating

²²⁵ Iressa Benefits Rise to the Top. *Med. Ad. News*, August 2003. FDA. Label of Gefitinib as of May 5, 2003. www.fda.gov, accessed Oct 2008.

²²⁶ Fuhrmans, V. How to Get New -- but Unapproved -- Drugs --- Under Pressure, Companies Offer More Treatments for 'Compassionate Use'. *Wall Street Journal*, December 5 2002.

and life-threatening disease”.²²⁷ Such reasoning stood in arguable conflict with the results of two large, controlled, randomized clinical trials on first-line treatments of NSCLC, which had shown no benefit from adding gefitinib to standard chemotherapy.²²⁸ An article in *The Wall Street Journal*, titled ‘FDA to Patients: Drop Dead’, commented on these trials: arguing that studies and data could always be better, the article claimed the presence of negative study results “not [to be] a good reason, and certainly not an ethical one, for delaying approval”.²²⁹ The article continued to explain that particularly in cases of terminal disease, “any safe drug with even a “hint” of effectiveness should be brought to market as quickly as possible” in order to save or extend some lives immediately. Such action, the article pointed out, would also “give doctors the chance to discover uses far beyond what the FDA originally envisioned”.²³⁰

On this background, in September 2002, a FDA advisory panel composed of prominent oncologists voted 11 to 3 to recommend the accelerated approval of gefitinib as third-line treatment for patients with stage III or IV NSCLC, who had not responded to conventional chemotherapy.²³¹ The panel argued that gefitinib fulfilled the approval requirements despite the concerns about the drug’s overall efficacy raised by AstraZeneca’s larger trials mentioned above, because the drug appeared to have helped at least some desperately ill lung cancer patients.²³² The panel member John T. Carpenter Jr. of the University of Alabama explained his decision, “it’s very clear that some people are getting better and some people are getting clinical benefit”.²³³ The panel chairwoman Donna Przepiorka reasoned, “I’ve never seen a lung cancer patient whose cancer went away by itself. Very clearly there are patients whose cancer went away with

²²⁷ AstraZeneca Announces US Label Change for IRESSA (gefitinib) and New Distribution Program. *PR Newswire*, June 17 2005.

²²⁸ FDA. Label of Gefitinib as of May 5, 2003. www.fda.gov, accessed Oct 2008.

²²⁹ FDA to Patients: Drop Dead. *Wall Street Journal*, September 24 2002.

²³⁰ *Ibid.*

²³¹ Pollack, A. Federal Advisory Panel Backs New Cancer Drug. *New York Times*, September 25 2002. The Cancer Drug Delay. *Wall Street Journal*, January 16 2003.

²³² Pollack, A. Federal Advisory Panel Backs New Cancer Drug. *New York Times*, September 25 2002.

²³³ *Ibid.*

Iressa.”²³⁴ In its recommendation to approve gefitinib, the panel considered the drug’s to that date unique mechanism of action and the virtual absence of medical treatment strategies for advanced NSCLC. As described under the section on the new drug laws of the late 1980s and early 1990s, the fatality of a disease and the lack of alternative treatments were important criteria for accepting a drug into accelerated approval tracks.

Despite its panel’s arguments, the case of gefitinib’s approval posed a dilemma for the FDA, because the larger studies, known as the intact trials, had already shown gefitinib not to provide any benefit when used as initial therapy. A FDA reviewer asked, “can FDA consider accelerated approval when it has already been demonstrated in the intact trials that there is no survival advantage?”²³⁵ The situation became even more complicated in December 2002, when reports of interstitial lung disease in lung cancer patients receiving gefitinib in Japan prompted the Japanese Ministry of Health, Labor and Welfare to introduce strict precautions on gefitinib’s use.²³⁶ Interstitial lung disease (ILD) is characterized by global inflammation, scarring and tissue damage in the lungs. Of the patients, who had been taking gefitinib and had developed ILD, about one-third had died as a direct consequence of the ILD.²³⁷

Given the complexity of gefitinib’s case, the FDA postponed its review deadline from February 5 to May 5 2003.²³⁸ The FDA intended to use the additional time in order to scrutinize the Japanese cancer patient deaths. Director of the Office of Drug Evaluation at the FDA, Robert J. Temple, explained, “we worried about that and took some extra time to review it while the company pulled data together”. Temple further pointed to how little was known at the time about the ILD cases in Japan. The FDA only knew that the Japanese postmarketing experience

²³⁴ *Ibid.*

²³⁵ Pollack, A. FDA Staff Voices Doubts on AstraZeneca Cancer Drug. *New York Times*, September 24 2002.

²³⁶ Humphreys, A. Ability to Manage. *Med. Ad. News*, September 2003.

²³⁷ Iressa Benefits Rise to the Top. *Med. Ad. News*, August 2003.

²³⁸ The Cancer Drug Delay. *Wall Street Journal*, January 16 2003.

demonstrated about a 2% rate of ILD with gefitinib use.²³⁹ It lacked detailed information on the actual incidents and on comparative rates in the United States or other countries. Upon the review of U.S. data, however, the FDA soon determined the rate of ILD in a large, U.S. based, expanded-access program of gefitinib to be approximately 0.3%. Worldwide, the rate of ILD with gefitinib use was reported as about 1%. Thereupon, the FDA concluded that the rate of ILD in Japanese patients had not been replicated in the United States.²⁴⁰

AstraZeneca responded to the Japanese and the FDA's findings with the assertion of attempting to determine why the rate of ILD was higher in Japan than anywhere else. However, as pointed out by Mary Lynn Carver, the director of oncology public affairs at AstraZeneca, just because ILD occurred at all should not have deterred U.S. oncologists from prescribing gefitinib. According to Ms. Carver, "interstitial lung disease is something that Western oncologists are very familiar with and used to dealing with because it is something that does appear in advanced lung cancer patients regardless of what treatment they receive".²⁴¹

The Wall Street Journal argued along similar lines, claiming that conventional chemotherapy had much higher rates of potentially fatal side-effects compared to gefitinib. As evidence for this statement, the newspaper pointed to the apparent lack of a letup in the demand by physicians for gefitinib. According to *The Wall Street Journal*, the number of patients in the United States who had received gefitinib through compassionate use programs had surpassed 20,000 by January 2003. The newspaper also stressed that authorities and physicians in other countries were not impressed by the ILD rates in Japan and continued to call gefitinib a "miracle drug". *The Wall Street Journal* quoted Kenneth Tsang Wah-tak of the University of Hong Kong, "bear in mind that lung cancer patients could die of serious complications such as pneumonia due

²³⁹ Iressa Benefits Rise to the Top. *Med. Ad. News*, August 2003.

²⁴⁰ *Ibid.*

²⁴¹ *Ibid.*

to poor immunity or the side effects of other cancer treatments”.²⁴² The newspaper then continued to harshly criticize the FDA, “if only we could import such common sense for the FDA”.²⁴³ *The Wall Street Journal* accused the FDA of using the relative risk of gefitinib as a “delaying tactic” in the drug’s approval. It pointed out that all drugs had side effects and contra-indications and posed the rhetoric question “should aspirin be reconsidered just because an ulcer sufferer might take it?”²⁴⁴ Furthermore, the newspaper saw “FDA’s dithering on Iressa” as part of a general “disturbing pattern”.²⁴⁵ It argued that FDA review times had increased recently due to such delay mechanisms, “the agency claims the average approval time for the 17 new drug compounds (new molecular entities in FDA parlance) it cleared in 2002 was 15.2 months, down from 18.5 months in 2001 and 17.2 in 2000. But six of those drug applications were refilings, which started the clock all over again and artificially shortened the average ... Not counting such refiled applications, average approval time in 2002 was actually longer than in previous years.”²⁴⁶ It concluded that the “notoriously arrogant and defensive FDA”²⁴⁷ was sending “the unfortunate message” of “back off” to oncologists who were “desperate in the fight against the disease”.²⁴⁸ According to *The Wall Street Journal*, “the FDA should view itself not as a gatekeeper but as a facilitator”.²⁴⁹ Considering all the measurements implemented since the late 1980s, which intended and effectively managed to decrease FDA drug approval times, it almost appears as if the process of drug approval could never be fast enough for certain entities such as *The Wall Street Journal*.

Not surprisingly, the pharmaceutical industry agreed with *The Wall Street Journal*’s painting of the situation, although its official representatives did not demonstrate the same kind of

²⁴² The Cancer Drug Delay. *Wall Street Journal*, January 16 2003.

²⁴³ *Ibid.*

²⁴⁴ *Ibid.*

²⁴⁵ *Ibid.*

²⁴⁶ *Ibid.*

²⁴⁷ Revolution at the FDA. *Wall Street Journal*, February 19 2003.

²⁴⁸ The Cancer Drug Delay. *Wall Street Journal*, January 16 2003.

²⁴⁹ Revolution at the FDA. *Wall Street Journal*; February 19 2003.

outspokenness. The chief executive of the pharmaceutical firm Genta, Raymond P. Warrell Jr., for example, charged, “the rigidity with which the survival hammer has been applied in the past was much too extreme. Are you going to reject a drug that has shown clear benefits because of a regulatory standard that has migrated over the last few years?”²⁵⁰ Thereby, he referred to the clinical trial end points of life-extension or -enhancement versus surrogate markers such as tumor shrinkage.

Richard Pazdur, director of the FDA’s division of oncology-drug products, countered such accusations by pointing to the markedly shorter FDA review times in the early 2000s for potentially life-saving or life-extending drugs relative to previous years. According to Pazdur, drug approval times had been shortened, even though the FDA attempted to preserve consumer protection goals. In his view, the latter was a crucial role of the FDA. He argued, “I believe we are more reasonable in trying to get drugs out to patients”, adding “we can’t be in the position of potentially approving a placebo”.²⁵¹

On May 5 2003, the FDA approved gefitinib in an accelerated process. It did so on the basis of the small, uncontrolled phase II trial mentioned above, which had shown a tumor shrinkage of more than 50% in 10.6% of patients, who had previously failed conventional chemotherapy. According to the FDA, the approval was granted because of the low survival rate of advanced NSCLC patients and the lack of effective medicines for these patients. FDA commissioner Mark B. McClellan commented, “FDA believes it is crucial for cancer patients to have many safe and effective treatment options available to them in their battle against this disease. With the approval of Iressa, thousands of patients with lung cancer will now have access to an additional treatment after others haven’t worked to stop the progression of their disease.”²⁵²

²⁵⁰ Wilde Mathews, A. Are Long Trials Always Needed for New Drugs? *Wall Street Journal*, April 26 2004.

²⁵¹ *Ibid.*

²⁵² Iressa Benefits Rise to the Top. *Med. Ad. News*, August 2003.

Many cancer patients and physicians were pleased with the FDA's decision, as was AstraZeneca. In the first half of 2003, Iressa sales totaled \$66 million, including \$18 million in U.S. sales after the drug's launch in mid May. More than 37,000 American patients with NSCLC had received gefitinib through the preapproval expanded access program, and by the end of June, an estimated 10,000 patients were taking gefitinib in the United States.²⁵³ In 2003, financial analysts predicted yearly Iressa sales of \$850 million by 2007, thereby rendering Iressa a significant contributor to AstraZeneca's product cycle.²⁵⁴

However, the approval of Iressa also prompted several critical voices to speak up. Amongst the critics of gefitinib's accelerated approval was the Public Citizen advocacy group. Public Citizen criticized the study which had resulted in the drug's approval, arguing that the study involved an atypical subset of patients with less aggressive cancers, lacked adequate controls, and did not separate the effects of the drug from the effects of other medications the patients were taking.²⁵⁵ The group also called for a black-box warning to prevent gefitinib's use as a first-line treatment for NSCLC. Black-box warnings were a type of warning that appeared on the package insert of prescription drugs. A black-box warning indicated the presence of substantial evidence for serious or even life-threatening side effects. It was the strongest warning that the FDA could require on a prescription drug.²⁵⁶ Public Citizen wanted to restrict the drug's use to the kind of patients who had been studied in the phase II trial, which approval had been based on. Furthermore, the black-box warning should include information about interstitial lung disease. The FDA rejected the request for a black-box warning for gefitinib because of the lack of alternatives available to NSCLC patients who had failed conventional chemotherapy.²⁵⁷

²⁵³ Humphreys, A. Ability to Manage. *Med. Ad. News*, September 2003.

²⁵⁴ *Ibid.*

²⁵⁵ Mitka, M. 2003. Accelerated Approval Scrutinized: Confirmatory Phase 4 Studies on New Drugs Languish. *JAMA*. 289:3227-3229.

²⁵⁶ www.wikipedia.org, accessed February 2009.

²⁵⁷ Iressa Benefits Rise to the Top. *Med. Ad. News*, August 2003.

Thomas Fleming, a biostatistician at the University of Washington and a member of the FDA's Center for Drug Evaluation and Research's Oncologic Drugs Advisory Committee, explained why he voted against gefitinib's approval, "as I indicated at the committee meeting, at the time, I quite strongly opposed the approval, either full or accelerated, based on my concern that there was not evidence of efficacy". Referring to what he perceived as troubling evidence for the failure of pharmaceutical companies to meet the conditions attached to the accelerated approval of drugs, Fleming continued, "what has taken place since that time has only reinforced that perspective".²⁵⁸ Thereby, Fleming extended his critic from the approval of gefitinib to accelerated approval processes in general. By receiving accelerated approval for a drug, the manufacturer was committed to carry out additional postmarketing or phase IV clinical trials to determine whether the drug conferred a real clinical benefit. Fleming was concerned that many phase IV trials never took place or only with much delay, and he questioned how real the FDA's threat of market withdrawal in absence of efficacy data was. To substantiate his concerns, Fleming pointed to eight oncology drugs, which had been granted accelerated approval and whose follow-up studies were expected to take at least 10 years with no guarantee of ever producing meaningful results.²⁵⁹ None of these drugs were likely to be taken off the market. As one of the causes for the delay in postmarketing trials, Fleming identified the difficulty to enroll enough patients in phase IV trials. He referred to the low incentives of patients to take part in phase IV trials, where they would be randomized into treatment and control groups, whilst they had the alternative of getting the drug on the market. However, even more importantly, Fleming reasoned, drug manufacturers felt a reduced sense of urgency to complete follow-up studies for drugs approved under the accelerated pathway. According to Fleming, "sponsors, particularly industry sponsors, have a keen sense of urgency to develop an agent in a timely fashion, but once the agent is approved, there is almost a reverse motivation – you'll market the product until it's shown not

²⁵⁸ Mitka, M. 2003. Accelerated Approval Scrutinized: Confirmatory Phase 4 Studies on New Drugs Languish. *JAMA*. 289:3227-3229.

²⁵⁹ *Ibid.*

to work”.²⁶⁰ Fleming further explained that “no one would tolerate that in a premarket setting, but now there’s a clear sense of loss of urgency”. With respect to the market withdrawal of drugs, Fleming charged, “even when agents have been studied in confirmatory trials where benefit wasn’t established, there is a lack of a clear strategy of plan in the FDA oncology department on how to proceed – the FDA continues to allow marketing of the product”.²⁶¹

According to Robert J. Temple, the director of the Office of Drug Evaluation at the FDA, a drug approved under the accelerated pathway had to be removed from the market if follow-up clinical studies failed to demonstrate a real benefit. However, Temple admitted that the FDA viewed the market withdrawal of a drug very cautiously, “when a drug has proved active in a setting where nothing else worked, you don’t lightly remove it because a trial failed to show overall survival effect. You try to do other studies. You think about why the studies failed.”²⁶² Temple acknowledged that up until that time, no product on the market had ever been removed because no benefit could be established in follow-up studies.²⁶³

Countering the charge of absent or delayed phase IV clinical trials, Richard Pazdur, the director of oncology-drug products at the FDA, raised the argument of follow-up studies being “only one aspect of accelerated approval”, despite an “extremely important” one.²⁶⁴ He pointed out that “the life of a drug is very complicated and has many avenues to demonstrate clinical benefit, including the practical use in the community”.²⁶⁵ The director of the FDA’s Office of New Drugs, John Jenkins, provided some numbers on the delay of phase IV trials: in September 2003, half of all accelerated approval drugs had completed postmarketing studies, 28% had not

²⁶⁰ *Ibid.*

²⁶¹ *Ibid.*

²⁶² *Ibid.*

²⁶³ Iressa Benefits Rise to the Top. *Med. Ad. News*, August 2003.

²⁶⁴ Mitka, M. 2003. Accelerated Approval Scrutinized: Confirmatory Phase 4 Studies on New Drugs Languish. *JAMA*. 289:3227-3229.

²⁶⁵ *Ibid.*

yet begun, and 1.6% were officially delayed.²⁶⁶ With respect to cancer drugs, Charles L. Bennett, a professor of medicine at Northwestern University, reported follow-up data to have been submitted in only 9 cases out of 26 accelerated approvals. Furthermore, in one of his surveillance studies, Bennett found eight examples of serious side effects discovered after the drugs were on the market, thereby indicating an inherent safety problem with the accelerated approval process.²⁶⁷

Similar criticism as outlined above has also been raised in many scientific and clinical journals, including an editorial in the *Journal of Clinical Oncology* titled ‘Hurry Up and Wait: Is Accelerated Approval of New Cancer Drugs in the Best Interests of Cancer Patients?’²⁶⁸

Proving some of the concerns mentioned above wrong, AstraZeneca conducted timely postmarketing studies. In December 2004, the company released its results, which failed to show statistical significance for survival in patients receiving gefitinib as compared to patients receiving a placebo.²⁶⁹ In response to these findings, the FDA scheduled an oncology advisory panel meeting for March 2005. When AstraZeneca heard of the planned meeting, the company suspended the promotion of Iressa in the United States and withdrew its marketing application with European regulatory authorities.²⁷⁰ In June 2005, the FDA initiated label changes for gefitinib, which restricted its use to patients who had previously taken it and were benefiting from the drug. In addition, gefitinib was to be available for use in clinical trials. However, the drug was

²⁶⁶ *Ibid.*

²⁶⁷ Pollack, A. FDA Panel Weighs Fate of a Drug for Cancer. *New York Times*, March 5 2005.

²⁶⁸ Schilsky, R. 2003. Hurry Up and Wait: Is Accelerated Approval of New Cancer Drugs in the Best Interests of Cancer Patients? *J. Clin. Oncol.* 21:3718-3720.

²⁶⁹ FDA. Label of Gefitinib as of June 17, 2005. www.fda.gov, accessed October 2008. VanArnum, P. FDA: Drug Approval Process Under the Microscope. *Chemical Market Reporter*, March 14 2005.

²⁷⁰ VanArnum, P. FDA: Drug Approval Process Under the Microscope. *Chemical Market Reporter*, March 14 2005.

removed from the market for new patients: after September 15 2005, no new patients were allowed access to gefitinib unless they were part of a clinical study.²⁷¹

Maha H. A. Hussain, an advisory panel member and a professor at the University of Michigan, explained the FDA's difficult position, "ethically, it's going to be very hard to say to a patient who's on it [gefitinib] and is responding, or is likely to respond when there is nothing else, that you can't get it. On the other hand, I think it's also unethical to keep it available for people who we know are not likely to benefit."²⁷² Hence, the FDA settled on a compromise as outlined above. Thereby, the availability of Tarceva, a drug with a very similar mechanism of action as Iressa, facilitated the FDA's decision to limit access to Iressa. Unlike Iressa, Tarceva, which was developed and marketed by OSI Pharmaceuticals and Genentech, had demonstrated improved survival in clinical studies on NSCLC.²⁷³

Not surprisingly, the FDA's action prompted different kinds of responses. Many patients were distressed about gefitinib's market withdrawal for new patients. Laurie Fenton, president of the Lung Cancer Alliance, a patient advocacy group, thought it unrealistic to expect a drug, which provided tremendous benefits for a small subset of patients, to be proven effective for the entire lung cancer population.²⁷⁴ She asked, "what about a new patient who has washed out of all other options? Why should Iressa not be made available to them?"²⁷⁵ In line with Fenton and countering the FDA on the suggestion of using Tarceva instead of Iressa, a lung cancer specialist at the University of Colorado named Paul Bunn pointed to the small but nevertheless existing number of patients who could not tolerate Tarceva but could use Iressa.²⁷⁶ Steven Walker, advisor to the Abigail Alliance for Better Access to Developmental Drugs, called the limitation of access

²⁷¹ FDA. Label of Gefitinib as of June 17, 2005. www.fda.gov, accessed Oct 2008. AstraZeneca Receives FDA Approval for New Cancer Drug Iressa (gefitinib, ZD1839). *PR Newswire*, May 5 2003.

²⁷² Pollack, A. FDA Panel Weighs Fate of a Drug for Cancer. *New York Times*, March 5 2005.

²⁷³ Pollack, A. FDA Restricts Access of Cancer Drug, Citing Ineffectiveness. *New York Times*, June 18 2005.

²⁷⁴ Pollack, A. FDA Panel Weighs Fate of a Drug for Cancer. *New York Times*, March 5 2005.

²⁷⁵ Pollack, A. FDA Restricts Access of Cancer Drug, Citing Ineffectiveness. *New York Times*, June 18 2005.

²⁷⁶ *Ibid.*

to Iressa “entirely unnecessary”.²⁷⁷ He argued that physicians were already using Tarceva before Iressa and charged, “it appears the FDA is waging war on cancer patients instead of on cancer”.²⁷⁸

The company AstraZeneca maintained its assurance of gefitinib’s safety and stressed the postmarketing trial’s results for patients of Asian descent and patients who had never smoked. For this specific subset of lung cancer patients, the data suggested a statistically significant benefit of gefitinib. AstraZeneca was now looking at specific EGFR mutations, which might be associated with a clinical response to gefitinib. If such mutations were found, gefitinib could be approved specifically for patients with the mutations in question. Mary Lynn Carver from AstraZeneca concluded, “the science just needs to catch up in order for Iressa to have another chapter”.²⁷⁹

Groups like the Public Citizen, on the other hand, argued for the complete revocation of gefitinib’s approval whilst allowing existing users to continue their treatment in clinical trials.²⁸⁰ In early 2005, before the FDA’s decision on gefitinib’s fate, the group had filed a petition urging the FDA to exercise its authority by removing gefitinib entirely from the market. According to an analysis by the Public Citizen’s Research Group, gefitinib was linked to 83 deaths between May 2003 and September 2004.²⁸¹ Deputy Director of the Public Citizen’s Research Group, Peter Lurie, warned, “leaving Iressa on the market increases the likelihood that patients will be diverted from an effective therapy to an ineffective therapy, endangering their lives”.²⁸² He added, “keeping a drug on the market while effectively telling people to avoid taking it is not an adequate public health response”.²⁸³

Otis W. Brawley, an oncologist at Emory University and a member of the FDA’s panel evaluating gefitinib, pointed to the possibility of an erroneous approval in the first place.

²⁷⁷ *Ibid.*

²⁷⁸ *Ibid.*

²⁷⁹ *Ibid.*

²⁸⁰ *Ibid.*

²⁸¹ VanArnum, P. FDA: Drug Approval Process Under the Microscope. *Chemical Market Reporter*, March 14 2005.

²⁸² *Ibid.*

²⁸³ *Ibid.*

According to Brawley, gefitinib should not have been approved until it was better understood who could benefit. In Brawley's eyes "the development of this drug has been mishandled. It's been mishandled by AstraZeneca. It's been mishandled by this committee."²⁸⁴

In early 2005, discussions concerning the efficacy of AstraZeneca's Iressa, in conjunction with the recent withdrawal of the multiple sclerosis drug Tysabri and inquiries into the safety of COX-2 inhibitors, raised concerns among several politicians. Congressional hearings were held to examine the FDA's decision making capacity and to review the controversies regarding the approval process. During one of these sessions, Senator Mike Enzi, chairman of the Senate Health, Education, Labor and Pensions Committee, concluded, "we must not sacrifice safety to speed drugs to market."²⁸⁵ However, he also argued, "we must weigh benefits and risks on the same scale. As patients, every time we take a drug, we take a risk, so we should not overreact to recent events. Attempting to achieve a zero safety risk would block millions from benefiting from life-saving drugs and therapies."²⁸⁶ Enzi criticized the manner in which accelerated approval processes were carried through rather than the current drug regulations themselves. He even warned from reverting to a pre-1990s-reform system.

Furthermore, in June 2005, the Democratic Representative Edward J. Markey of Massachusetts, a senior member of the Energy and Commerce Committee, released a report on the current drug approval processes. Using gefitinib's case as evidence, Markey alleged a "conspiracy of silence" between the FDA and drug companies with respect to accelerated approval.²⁸⁷ Markey deemed this conspiracy responsible for a lack in detailed information on new drugs, "the public will never know if the products that they believe are safe and effective are no

²⁸⁴ Pollack, A. FDA Panel Weighs Fate of a Drug for Cancer. *New York Times*, March 5 2005.

²⁸⁵ VanArnum, P. FDA: Drug Approval Process Under the Microscope. *Chemical Market Reporter*, March 14 2005.

²⁸⁶ *Ibid.*

²⁸⁷ Drug Malarkey. *Wall Street Journal*, June 9 2005. Pollack, A. FDA Restricts Access of Cancer Drug, Citing Ineffectiveness. *New York Times*, June 18 2005.

better than sugar pills or may be even dangerous to their health”.²⁸⁸ Pazzur from the FDA acknowledged that the FDA was pressured by drug sponsors.²⁸⁹ However, he firmly believed in the FDA’s ability to withstand such pressures. According to Pazzur, the FDA knew that “the purpose of accelerated approval was not accelerated drug company profits”.²⁹⁰ In line with its previous statements calling for ever shorter approval times and minimal interference of the FDA after a drug’s marketing had been launched, *The Wall Street Journal* described Markey’s report as a “stunt to grab some media attention” and Markey himself as “the latest headline seeker”.²⁹¹

Presently, the biologic mechanism of gefitinib’s therapeutic action is still debated. According to current beliefs, the small molecule gefitinib binds and inhibits specific mutants of EGFR, and it is cancer patients with these mutations which respond to the drug.²⁹²

²⁸⁸ Drug Malarkey. *Wall Street Journal*, June 9 2005.

²⁸⁹ Mitka, M. 2003. Accelerated Approval Scrutinized: Confirmatory Phase 4 Studies on New Drugs Languish. *JAMA*. 289:3227-3229.

²⁹⁰ The FDA Versus Cancer Patients. *Wall Street Journal*, May 19 2005.

²⁹¹ Drug Malarkey. *Wall Street Journal*, June 9 2005.

²⁹² Dowell, J., and Minna, J. 2005. Chasing Mutations in the Epidermal Growth Factor in Lung Cancer. *N. Engl. J. Med.* 352:830-832. Marshall, J. 2006. Clinical Implications of the Mechanism of Epidermal Growth Factor Receptor Inhibitors. *Cancer*. 107:1207-1218. Khuri, F., and Roman, J. 2008. From Nihilism to Individualism: The Evolution of Lung Cancer Therapy. *Am. J. Respir. Crit. Care Med.* 177:1299-1300. Silvestri, G., and Rivera, M. 2005. Targeted Therapy for the Treatment of Advanced Non-Small Cell Lung Cancer: A Review of the Epidermal Growth Factor Receptor Antagonists. *Chest*. 128:3975-3984. Sohn, E. 2005. Targeted Attack. *Science News*. 139-140. Roses, A. 2008. Pharmacogenetics in Drug Discovery and Development: A Translational Perspective. *Nat. Rev. Drug Discov.* 7:807-817.

8. Conclusion

For decades the tension between drug safety and drug availability has engaged the public, the government, physicians and the pharmaceutical industry. Drug safety could be enhanced by long and extensive pre-approval studies and the careful and thorough review of all trial results prior to a drug's marketing. Invariably, such measures would result in long approval times and the slow marketing of drugs. Drug availability, on the other hand, could be increased by shifting clinical trials to the postmarketing phase, assigning much of the control over drug safety and efficacy to physicians and the pharmaceutical industry instead of the FDA, and by shortening the drug review process. Such measures could make potentially life-saving and life-enhancing drugs rapidly accessible to patients at the expense of an increased risk of drug toxicity and inefficacy.

Focusing exclusively on drug availability increased the risk of commission or of approving a harmful drug, of which the most prominent example was thalidomide (at least in Europe where it had been approved). On the other hand, emphasizing mainly drug safety raised the risk of omission or of failing to approve a helpful drug, of which sodium valproate might be an example. Both, commission and omission mistakes could cause the death of patients and ought to be avoided. Hence, the basic debate centered on where the right balance lay between drug availability and drug safety, between short and long drug approvals, between higher risks of commission mistakes or omission mistakes. Or as phrased at the beginning of this essay: how slow is too slow, how fast is too fast?

Before 1962, the discoveries of life-saving antibiotics laid an emphasis on drug availability and the rapid marketing of drugs, thereby raising the risk of commission mistakes. On the background of the thalidomide crisis, the 1962 Kefauver-Harris Amendments reframed the issue of drug approval, giving it heavy tendencies towards the drug safety end of the spectrum. This was achieved by introducing stricter regulations on the pharmaceutical industry and by

broadening the FDA's authority. In response, the pharmaceutical industry and many physicians warned from a decrease in drug innovation and drug availability and from an increased risk of omission mistakes. The American pharmaceutical industry feared a drop in profits and a reduction in their competitiveness on the international drug market. Many physicians resented the FDA's new control over drug efficacy, which used to be their field of expertise. Furthermore, physicians were concerned that slow new drug introductions would deprive their patients of life-saving measures.

During the 1970s, the term 'drug lag' was coined. The expression, inherently biased toward drug availability, was rapidly promoted by pharmaceutical companies, physicians and by conservative parties. It was used to reframe the question of drug approval and to fight governmental regulations on industry. Furthermore, on the background of general consumer movements and widespread criticism of medical practice and the "half-Gods in white"²⁹³, patient organizations made their voices heard. As illustrated by the case of sodium valproate, patients, too, used the notion of 'drug lag' as a political weapon to argue against government regulations. On the surface, the public opposition against a governmental institution which aimed to ensure public safety might seem surprising and unusual. However, in the light of the 1970s challenge of medical authority, patients' fight against medical and the FDA's paternalism appears less perplexing. Like the pharmaceutical industry and conservative associations, patient organizations demanded the faster marketing of new drugs, hoping for quicker access to life-enhancing or life-saving measures.

In the context of the Reagan Administration's emphasis on deregulation and a public health crisis caused by the emergence of AIDS, the political pressure on the FDA rose enormously. The attitude had shifted from favoring a lower risk of commission to preferring a lower risk of omission. Eventually, the drug regulations were revised with the aim to reduce the

²⁹³ Nelson Pill Hearings, 1970.

time required to market a new drug of potential therapeutic benefit for life-threatening or serious diseases. Whereas the pharmaceutical industry and many AIDS organizations welcomed the new regulations, many scientists, physicians and some AIDS activists viewed the revisions very critically. They feared a marked increase in commission mistakes with the accelerated approval procedures and the new reductions in pre-approval standards for drug safety and efficacy. Furthermore, concerns were raised about the ability of scientists and physicians to obtain detailed information on a drug approved under the accelerated pathway. Indications of delays in the completion of phase IV or postmarketing studies and doubts on the FDA's determination to withdraw drugs from the market in the absence of timely efficacy data from follow-up studies further added to the fears and concerns of these critical voices. Their arguments stood in marked contrast to the pharmaceutical industry's and conservative parties' perspective, both of which demanded even faster market access for new drugs, going as far as suggesting a limitation of the FDA's authority to merely certifying new drugs without any control over the marketing of experimental drugs.

Relative to the 1962 Amendments, the revised regulations of the 1980s and 1990s strongly emphasized drug availability. The pendulum had swayed from focusing on drug safety to focusing on market availability. This development had relied heavily on the notion of a 'drug lag' in the United States. The invention of the term 'drug lag' can thus be viewed as a successful weapon in fighting governmental regulations on the pharmaceutical industry.

Recent drug cases such as gefitinib and rofecoxib (Vioxx) renewed and reinforced the critiques of the revised regulations. Both, gefitinib and rofecoxib had to be withdrawn from the market at least partially for safety and efficacy reasons. Rofecoxib, an anti-arthritic agent of the COX-2 inhibitor family of drugs, was approved by the FDA in 1999. As early as in 2000, a study

known as VIGOR linked the drug to increased cardiovascular incidents.²⁹⁴ However, it was not until 2004 that rofecoxib was withdrawn from the market because of its cardiovascular toxicity. According to a study by the FDA, between 88,000 and 139,000 patients in the United States had suffered from a myocardial infarction or a stroke secondary to the use of rofecoxib before the drug's withdrawal. Thereby, the cardiovascular incidents related to rofecoxib carried a mortality of 30-40% and even higher rates of severe morbidity.²⁹⁵ Furthermore, the legal trials following the Vioxx crisis revealed that the drug's manufacturer Merck had withheld negative study results. More specifically, in 2001, Merck had omitted to submit data to the FDA, which demonstrated a statistically significant increase in mortality in patients receiving rofecoxib versus patients receiving placebo.²⁹⁶ Moreover, during an extensive analysis of 250 scientific papers on rofecoxib, numerous articles were identified, which had been published under the names of distinguished and renowned scientists and physicians, so called "opinion-leaders". However, the entire work, including the texts themselves, was Merck's very own production with no input from the famous scientists, under whose authorship the papers had appeared.²⁹⁷ According to the physician and industry-critic Etzel Gysling, Merck's attempt to have influential and seemingly independent "opinion leaders" present their data, insinuated unwarranted objectivity and constituted intentional deception.²⁹⁸ Of note, such actions were by no means restricted to rofecoxib or Merck. The practices of guest authorship and ghostwriting were (and are) widely

²⁹⁴ Bombardier, C., Laine, L., Reicin, A., et al. 2000. Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis. VIGOR Study Group. *N. Engl. J. Med.* 343:1520-1528. Gysling, E. 2005. Ceterum Censeo: Vioxx: Eine Wende? *Pharma-Kritik*. FDA. Label of Rofecoxib as of 2004. www.fda.gov, accessed October 2008.

²⁹⁵ Gysling, E. 2005. Ceterum Censeo: Vioxx: Eine Wende? *Pharma-Kritik*.

²⁹⁶ Psaty, B., and Kronmal, R. 2008. Reporting Mortality Findings in Trials of Rofecoxib for Alzheimer Disease or Cognitive Impairment: A Case Study Based on Documents from Rofecoxib Litigation. *JAMA*. 299:1813-1817. Gysling, E. 2008. Ceterum Censeo: Der Niedergang der Pharmaindustrie. *Pharma-Kritik*.

²⁹⁷ Ross, J., Hill, K., Egilman, D., and Krumholz, H. 2008. Guest Authorship and Ghostwriting in Publications Related to Rofecoxib: A Case Study of Industry Documents from Rofecoxib Litigation. *JAMA*. 299:1800-1812. Gysling, E. 2008. Ceterum Censeo: Der Niedergang der Pharmaindustrie. *Pharma-Kritik*.

²⁹⁸ Gysling, E. 2008. Ceterum Censeo: Der Niedergang der Pharmaindustrie. *Pharma-Kritik*.

endorsed and applied by the entire pharmaceutical industry.²⁹⁹ Critical voices of the 1990s drug regulations argued that an emphasis on drug safety with extensive pre-approval studies and careful data reviews would have prevented such practices from remaining unnoticed and patients from dying unnecessarily. Together with the case of gefitinib, the rofecoxib case prompted arguments of a current approval process, which was too fast.

Given this background, what are the arguments for an emphasis on drug availability in 2009? And what are the arguments for an emphasis on drug safety in 2009?

From the pharmaceutical industry's perspective, increased drug availability with shorter approval and marketing times mean increased short-term profits also in 2009 just as in the decades beforehand. Similarly, physicians in 2009 argue like doctors did in previous years and decades, namely that rapid access to new drugs might improve the health of some of their patients. Furthermore, a heavy focus on drug availability would shift much of the authority over drug safety and efficacy to physicians, a desirable outcome in many physicians' eyes also in 2009.

Starting in the 1970s, disease-specific patient organizations have become major advocates for rapid access to new drugs. Their argument lies in the devastating nature of omission mistakes. In their eyes, it is just as bad to impede a patient's hope for a cure as it is to unknowingly cause harm by giving a patient a poorly-studied drug. In 2009, there are more than 3,100 disease-specific advocacy groups, which press the FDA for rapid drug approvals. Unlike the patient organizations of the 1970s, however, most disease-specific advocacy groups in 2009 receive substantial funding from the pharmaceutical industry. The American Cancer Society, for example, receives seven to eight million dollars annually from pharmaceutical companies. The Marti

²⁹⁹ Krimsky, S. 2007. When Conflict-of-Interest Is a Factor in Scientific Misconduct. *Med. Law.* 26(3):447-463. Angell, M. 2004. *The Truth About the Drug Companies: How They Deceive Us and What To Do About It.* New York: Random House.

Nelson Cancer foundation, a small cancer-patient advocacy group based in Northern California, draws half of its revenue from industry.³⁰⁰

Whether such industry-consumer collaborations influence the patient organizations' focus on drug availability or simply allow the advocacy groups to make their voices heard can be argued about. The patient organizations themselves stress their independence from the pharmaceutical industry. Mike Katz from the International Myeloma Foundation, which obtains \$200,000 annually from drug companies, pointed out, "the notion that a person with an active disease or an incurable disease is going to either approve a drug that's a bad drug, just to help the company that's making the donation, or block approval of a competing drug because he doesn't want the company that funds his foundation to get injured – that is kind of ludicrous".³⁰¹ Nevertheless, at least one member of a patient organization, namely Nancy Roach from the Marti Nelson foundation, admitted that there might be some undue influence from the pharmaceutical industry, "they [the drug companies] will put advocates in a room. They'll say, 'Look at this data, the FDA is holding [a drug] up.' But you're only seeing part of the story."³⁰² Roach further acknowledged the industry's interest in patient advocates because of the political pressure, which patient organizations could create.

Whatever the influences on disease-specific advocacy groups by the pharmaceutical industry, their pleas are earnest and are based on the sincere hope to cure some devastating disease. A different story is the approval of so-called life-style drugs such as Botox, Viagra, and Propecia (approved in 1997 for the treatment of male-pattern baldness). The marketing of these drugs could not happen fast enough for some members of the public. When the attorney and citizen activist Ralph Nader published his book 'Unsafe at Any Speed: The Designed-In Dangers of the American Automobile' in 1965, many Americans expressed dismay. They preferred fast,

³⁰⁰ Hawthorne, F. 2005. *Inside the FDA: The Business and Politics Behind the Drugs We Take and the Food We Eat*. New Jersey: John Wiley & Sons, p. 121.

³⁰¹ *Ibid.*, p. 121.

³⁰² *Ibid.*, p. 202.

good-looking, and cheap cars over safe ones. Similarly, many patients now prefer the rapid access to life-style drugs over the drugs' verified safety.³⁰³

Further arguing for an emphasis on drug availability with approvals already after relatively small, quick and cheap clinical trials is the issue of drug safety versus drug cost. Cancer drug regimens, for example, can easily amount to \$160,000 annually per person.³⁰⁴ According to the pharmaceutical industry, high drug prices in the United States reflect the immense expenses in research and development and especially also the exorbitant costs of clinical trials, frequently quoted around \$1.2 billion per drug.³⁰⁵ Critics of the drug industry challenge this argument by pointing to the enormous proportion of drug companies' income – sometimes estimated at 80% –, which goes to advertising, management and profit margins.³⁰⁶ However, if the drug manufacturers are to be believed, then one might dispute a focus on drug safety at the expense of high drug costs by asking questions like Jerry Mande, former aide to vice-president Al Gore and to the FDA's commissioner Kessler: "If patients can't afford a new cancer drug, can that drug be said to be truly effective? And if not, is the FDA fulfilling its mandate to make sure drugs are effective?" Or like Dan Callahan of the Hastings Institute: "If people can die because they can't afford drugs, why isn't that as bad as the fact that people may die because some drugs are unsafe?"³⁰⁷ In practice, many consumers in the United States have found a solution to the problem of high drug prices by buying medications abroad or online, just like patients did in order to get access to non-FDA-approved drugs. Thereby, many American consumers are willing to buy drugs produced for countries with relatively low regulatory standards, demonstrating that affordable drugs are more important to them than high standards of drug safety.

³⁰³ Nader, R. 1965. *Unsafe at Any Speed: The Designed-In Dangers of the American Automobile*. Grossman Publishers.

³⁰⁴ Schrag, D. 2004. The Price Tag on Progress--Chemotherapy for Colorectal Cancer. *N. Engl. J. Med.* 351:317-319.

³⁰⁵ Malakoff, D. 2008. Clinical Trials and Tribulations: Spiraling Costs Threaten Gridlock. *Science.* 322:210-213.

³⁰⁶ Angell, M. 2004. Excess in the Pharmaceutical Industry. *CMAJ.* 171(12):1451-1453.

³⁰⁷ Hawthorne, F. 2005. *Inside the FDA: The Business and Politics Behind the Drugs We Take and the Food We Eat*. New Jersey: John Wiley & Sons, p. 289-290.

Having discussed several cases for focusing on drug availability, what are the arguments in favor of emphasizing drug safety in 2009? The FDA commissioner Jere Goyan alluded to several points supporting a focus on drug safety, ranging from an overmedicated society to the warranted distrust of physicians. Goyan repeatedly voiced his concerns over the American people, who were “looking to a pill for the answer to their problems”.³⁰⁸ Goyan criticized the tendency of American patients to take a pill for their hypertension or diabetes without worrying about anything else such as diet and exercise. According to Goyan, rapid access to many drugs did more harm to the American society than it did any good and definitely did not justify decreased safety standards for a drug’s approval.

Furthermore, Goyan deeply resented the thought of assigning physicians the authority over drug safety and drug efficacy after the accelerated approval of experimental drugs. Goyan doubted that physicians had the necessary competence to carry such powers. Thereby, Goyan’s doubts had been and continued to be substantiated by several drug incidents such as the anti-arrhythmics case of the 1980s. For almost a decade, physicians throughout the Western world had widely used these drugs, believing them to be highly beneficial. Cardiologists were so convinced of the benefit of anti-arrhythmics that they deemed the trials which tested anti-arrhythmics against placebo extremely unethical. At a meeting, they openly accused one of the trial leaders, “you are immoral” for “withholding” the drugs from some patients and giving them placebo instead.³⁰⁹ The results of the placebo-controlled studies came as a tremendous shock to physicians. They demonstrated a three-and-a-half-times greater death rate in patients on anti-arrhythmics compared to patients on placebo. At the time, some 400,000 patients received anti-arrhythmics annually to

³⁰⁸ *Ibid.*, p. 296.

³⁰⁹ Hilts, P.J. 2003. *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*. New York: Alfred A. Knopf, p. 231.

treat mild rhythm disturbances. An estimated 5000 patients had been killed annually by the drugs.³¹⁰

If their education and personal experience was not enough for physicians to achieve competence with respect to questions on drug safety and drug efficacy, one might argue that the professional literature could provide the required knowledge. The invalidity of this assumption is illustrated by the question of efficacy of the anti-depressives known as selective serotonin reuptake inhibitors or SSRIs. The FDA received 74 studies on the efficacy of SSRIs. 23 out of these 74 studies had never been published in professional journals. Of interest, 22 of the 23 non-published articles found no significant therapeutic benefit of SSRIs. Furthermore, 11 studies, which the FDA rated as showing unclear benefit, were published as papers demonstrating a beneficial effect of SSRIs. Hence, whereas only 51% of the studies analyzed by the FDA suggested SSRIs to be effective, the vast majority of the articles published in scientific and medical journals indicated clear therapeutic benefits of SSRIs.³¹¹ To anyone acquainted with the professional literature, the apparent proof of the SSRIs' efficacy must have seemed overwhelming. The bias observed in the professional literature can be enormous, precluding its use for purposes of achieving competency on drug safety and efficacy queries.

Moreover, the proposed inadequacy on the physicians' side also raises the question of a potential role of the FDA in controlling the off-label use of prescription drugs. Estimates on the frequency of off-label uses for prescription drugs in the United States center around 50%. So far, the FDA has no authority over what drugs are prescribed for. Thereby, safety tests for the on-label use of a certain prescription drug might not be transferrable to a different indication, be it because the new target population belongs to a different sex or age group, or be it because of different

³¹⁰ *Ibid.*, p. 231.

³¹¹ Turner, E., Matthews, A., Linardatos, E., Tell, R., and Rosenthal, R. 2008. Selective Publication of Anti-depressant Trials and Its Influence on Apparent Efficacy. *N. Engl. J. Med.* 358:252-260. Gysling, E. 2008. Ceterum Censeo: Der Niedergang der Pharmaindustrie. *Pharma-Kritik*.

dosing regimens, etc.³¹² Many SSRIs for example were (and are) frequently used off-label for teenagers, even though there was little data on the drugs' safety and efficacy in that age group and even though the developing brain of adolescents was thought to be physiologically different from adult brains. Over the course of several years, reports started to accumulate of increased suicidality in teenagers on SSRIs, resulting in warnings from the FDA about the use of SSRIs in children and adolescents. If the issue of drug safety is to be emphasized, then one might propose an extension of the FDA's authority to all uses of a drug, making off-label uses illegal. Of course, this would also mean that patients with poorly understood diseases, which have not been categorized yet and therefore do not have any drugs approved for them, could not be treated – unless the physician “changed” his diagnosis to one, for which the desired drug has been approved.

The parents of children who have committed suicide whilst taking an SSRI form a different kind of consumer group as the disease-specific patient organizations mentioned above. Such groups of drug-damaged patients and their families and friends constitute influential political organizations pleading for a focus on drug safety. They argue that commission mistakes are worse than omission mistakes, because the former are actively induced and change the natural process to the worse, whereas the latter simply prevent people from gaining an improvement without changing the natural course of their health. Furthermore, according to drug-damaged patients and their families, people looking for some risky treatment can always enroll in clinical trials or buy a drug abroad.

Interestingly, many scientists, including the ones involved in clinical trials, argue in favor of an emphasis on drug safety and extensive drug review. Not only do they feel a genuine need for the substantial proof of a drug's safety prior to its approval, but they also value the information gained from careful pre-approval trials on when and how exactly a drug should be

³¹² Frederick, R. 2008. Video: Pediatric Medicines--Prescribing Drugs "Off-Label". *Science*. 322:209.

used. Furthermore, several scientists have noticed an improvement in their operations after talking their projects over with FDA reviewers. The scientists point to the unique position of FDA reviewers, who have access to trial results from other, similar drugs, allowing them to make excellent suggestions on how to improve a certain study. Leigh Thompson from the drug company Eli Lilly, for example, recalled how in the development of one of the company's new ulcer drugs, the FDA reviewers had "suggested a radical change in protocol. That way, we were able to track how many [patients] had ulcers go away on the drug and come back on the placebo. The drug acted faster than we expected and wore off faster than we realized. We got much better data, and it didn't cost us more."³¹³ Hence, the careful review of clinical trials and their design does not only improve safety standards but also the quality of scientific operations.

A further argument for a focus on drug safety rather than drug availability lies in the vast number of "me-too" drugs, which are brought to the market. Between 1998 and 2003, 487 drugs received FDA approval. Of these, 379 were "me-too" drugs and 333 were old compounds in new formulations or combinations. Only 67 of the 487 approved drugs were new compounds, possibly able to add some therapeutic benefit over the existing panel of drugs already on the market. The remaining 420 drugs were unlikely to be of medical relevance, and there was no reason other than a drug manufacturer's profit to rush these drugs to the market.³¹⁴

Furthermore, with the birth of genetic engineering in the 1980s, the decoding of the human genome in 2003, and the establishment of the fields of genomics and proteomics, we are about to enter a new era of targeted drug therapy and personalized medicine. The drug gefitinib was one of the first targeted therapies approved by the FDA. In the age of personalized therapies, patients will be treated on the basis of their genetic susceptibilities and specific molecular mutations. According to a recent review in *Nature Reviews: Drug Discoveries*, pharmacogenetics,

³¹³ Hawthorne, F. 2005. *Inside the FDA: The Business and Politics Behind the Drugs We Take and the Food We Eat*. New Jersey: John Wiley & Sons, p. 135.

³¹⁴ Angell, M. 2004. Excess in the Pharmaceutical Industry. *CMAJ*. 171(12):1451-1453.

the study of genetic variations and their effects on the response to pharmaceutical agents, will play a “key role” in coming years.³¹⁵ With the possibility of performing genome-wide screens, drug companies will need to identify special patient subgroups for their drugs, as well as tests to quickly determine who falls into these subgroups and who does not. This is more complicated and more time-consuming than the generalized approaches to diseases of the past and present. Moreover, as indicated by the case of gefitinib, it may require more time than available under the accelerated approval process. In the light of the highly complex drug development processes in coming years, an emphasis on drug safety with stricter pre-approval guidelines and requirements for more extensive and longer pre-approval trials appears desirable.

Contrary to such reasoning, the pharmaceutical industry uses the case of gefitinib to argue for smaller, quicker and cheaper trials. Drug manufacturers maintain that personalized drugs should be judged differently from generalized drugs with respect to their proofs of safety and efficacy. According to the pharmaceutical industry, different standards for personalized drugs are warranted, because these drugs would be used only by a subset of patients with specific genetic characteristics. Within such a subset of patients, a targeted drug is expected to have an effect in up to 90% of cases. This in turn would allow for small clinical trials to show statistical significance. According to Garo Armen from the biotechnology company Antigenics Inc., “if a product works in 20 percent of subjects, and the control works in 10 percent, you need a large study, carefully designed, to capture that small difference in benefit. But if a product works in 90 percent, you’re going to see that in a very small trial. And if it’s targeted to work on a very specific pathway that’s relevant to your disease, by definition there will not be interactions with other pathways that do other things.”³¹⁶ By the latter, Armen attempted to justify a decreased need for safety proofs. In his article in *Nature Reviews: Drug Discovery*, Allen Roses from the Deane Drug Discovery

³¹⁵ Roses, A. 2008. Pharmacogenetics in Drug Discovery and Development: A Translational Perspective. *Nat. Rev. Drug Discov.* 7:807-817.

³¹⁶ Hawthorne, F. 2005. *Inside the FDA: The Business and Politics Behind the Drugs We Take and the Food We Eat*. New Jersey: John Wiley & Sons, p. 246.

Institute at the Duke University Medical Center further pointed to the potential improvement of the risk-benefit ratio during the process of clinical testing if patients were excluded from long-term clinical trials based on their DNA and adverse-event profiles and if efficacy studies were limited to patients expected to respond by pharmacogenetics. Thereby, Roses also stressed the financial incentives for pharmaceutical companies, which arose from such pharmacogenetics applications.³¹⁷ In his eyes, the technologies of pharmacogenetics offered marked advantages to patients and physicians in terms of improved drug safety and efficacy, as well as to the pharmaceutical industry by allowing for cheaper and quicker studies. According to Roses, pharmacogenetics permitted a focus on drug safety concomitant with an emphasis on drug availability. Both, Roses and Armen had to concede, though, that “we’re not there yet”³¹⁸ and their reasoning was based on a fair amount of speculation.

The FDA has responded to the new scientific advances by launching the so-called Critical Path Initiative, which comprised FDA guidelines and specific research projects aimed “to bring new scientific discoveries – in fields such as genomics and proteomics, tissue engineering, imaging, and bioinformatics – to bear on product development, to improve the accuracy of the tests we use to predict the safety and efficacy of investigational medical products”.³¹⁹

Finally, another argument for extensive pre-approval studies and longer drug reviews comes from increasingly complex political and ethical questions raised by the approval of certain therapies, such as embryonic stem cell therapies, abortion medicines, mind and body altering drugs like anti-depressants and growth hormones for short children, drugs that might facilitate certain behaviors such as the HPV vaccine Gardasil, which some fear to promote promiscuity in adolescents, and drugs that could end lives such as the infusions used for the death penalty. The

³¹⁷ Roses, A. 2008. Pharmacogenetics in Drug Discovery and Development: A Translational Perspective. *Nat. Rev. Drug Discov.* 7:807-817.

³¹⁸ Hawthorne, F. 2005. *Inside the FDA: The Business and Politics Behind the Drugs We Take and the Food We Eat*. New Jersey: John Wiley & Sons, p. 246.

³¹⁹ www.fda.gov/oc/initiatives/criticalpath/, accessed Oct 2008.

approval of such drugs raises questions far beyond drug safety and drug efficacy. Just because it is safe and effective to give short children growth hormone to promote further growth, does this mean that such a therapy should be approved and applied? Extensive and time-consuming political and ethical discussions are warranted, which in turn preclude a focus on drug availability and rapid drug marketing.

Finding the right balance between slow and fast drug approvals, between an emphasis on drug safety and drug availability is no easy task. From an emphasis on drug availability prior to 1962, the drug approval system shifted to a focus on drug safety with long and extensive pre-approval studies and reverted back to a more availability-focused system with mainly postmarketing surveillance. As illustrated by the case of gefitinib, the current system depends very heavily on postmarketing studies and thus relies on trust in the pharmaceutical industry's willingness to perform adequate surveillance studies and report also negative results. So far, the drug industry has not given many signs that it deserves such trust, as exemplified by the case of rofecoxib. It should be noted that the pharmaceutical industry's attempts to influence the drug approval process is just one way in which drug companies try to increase the marketing of their drugs. In her book *The Truth About the Drug Companies: How They Deceive Us and What to Do About It*, Marcia Angell outlines several other methods. Marcia Angell is a well known critic of the pharmaceutical industry who has been very influential in fighting industry-funding of researchers without disclosure. Despite the pharmaceutical industry's sometimes dubious behavior, it appears apparent that they are not solely responsible for the present concerns regarding the drug approval process. In 2009, the problem of drug approval is added further complexity from an increasing amount of interest groups, from extremely high drug costs, and from new and sometimes controversial technologies, the consequences of which are not clear yet. Nevertheless, or just because of this intricacy, the current strong focus on drug availability with its reliance on the pharmaceutical industry's ethical behavior seems inappropriate. The pendulum

has swayed too far into the direction of rapid drug marketing. A reframing of the issue of drug approval with more emphasis on careful pre-approval studies and extensive and thorough drug reviews seems warranted. Thereby, the question is not just one of drug regulations, but one of the best ways to serve the public interest.

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