Expediting Oncology Drug Approvals: The Public Backlash Against the FDA and Opportunities to Reform

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The Public Backlash Against the FDA and Opportunities to Reform

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Abstract

The FDA has made great strides over the past twenty years in loosening drug approval regulations to speed important, life-saving treatments to market. However, recent controversies involving anti-depressants for children and the withdrawal of two popular arthritis drugs and a multiple sclerosis therapy have created fears within the cancer community that the FDA will revert to a more cautious, conservative approval policy. Although cancer patient advocates have legitimate concerns about the pendulum swinging back to a more conservative agency stance, the FDA and the Oncologic Drugs Advisory Committee (ODAC) do not appear to have embraced a more risk-averse philosophy. Instead, the public backlash against the FDA presents the agency with an excellent opportunity to facilitate improvements to the accelerated approval and fast-track regulations for the benefit of cancer patients.

Introduction

Throughout its history, the Food and Drug Administration (FDA) has almost constantly endured criticism that drug approval processes in the United States are too slow, cumbersome and expensive.[1] In particular, the agency has been criticized for being too cautious and restrictive in approving life-saving drugs for people with terminal medical conditions.[2] The emergence of the Acquired Immune Deficiency Syndrome (AIDS) crisis in the 1980s generated substantial political pressure that forced the FDA to make significant policy changes to both expand access to experimental therapies and expedite approvals for drugs intended to treat life-threatening diseases.[3] Starting in the early 1990s, the agency implemented several mechanisms to facilitate and accelerate drug approvals in the United States, culminating in the formalization of these regulations in the FDA Modernization Act of 1997.[4] Despite the occasional misstep, the fast-track programs and accelerated approval regulations have been responsible for expediting the development, review, and approval of many important, life-saving drugs.[5] Cancer patients have been particularly fortunate as nearly a third of the sixty cancer drugs approved by the agency since 1995 have reached the market through accelerated approval mechanisms.[6] As a result, the FDA has been lauded for ensuring the safety and effectiveness of

[1] Christine Gorman, *Can the FDA Heal Itself?*, Time, Feb. 28, 2005, at 58.

[2] Dan Cray, *Balancing Act: Cutting Red Tape at the FDA Has Given a Big Boost to an AIDS-Fighting Biotech Firm*, Time, June 9, 1997, at 109; see also Michael D. Greenberg, *AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process*, 3 N.Y.U. J. Legis. & Pub. Pol'y 295, 306-07 (2000).

[3] Id. at 315-27.

[4] FDA Modernization Act, Pub. L. No. 105-115, § 101, 111 Stat. 2296, 2296-2305 (1997); see also Deborah G. Parver, *Expediting the Drug Approval Process: an Analysis of the FDA Modernization Act of 1997*, 51 Admin. L. Rev. 1249 (1999).

[5] Sheila R. Shulman and Jeffrey S. Brown, *The Food and Drug Administration's Early Access and Fast-Track Approval Initiatives: How Have They Worked?*, 50 Food & Drug L.J. 503, 505 (1995); see also Christopher-Paul Milne and Elaine Bergman, *Fast Track Product Designation Under the Food and Drug Administration Modernization Act: The Industry Experience*, Drug Information Journal, Jan./Mar., 2001, at 71; Tufts University Center for the Study of Drug Development, *FDA's Fast Track Initiative Cut Total Drug Development Time by 3 Years*, Impact Report, Nov./Dec. 2003, at 2 (hereinafter Tufts CSDD Fast-Track Study).

[6] Thomas G. Roberts, Jr. and Bruce A. Chabner, *Beyond Fast Track for Drug Approvals*, New England Journal of Medicine, Jul. 29, 2004, at 502; see also Richard L. Schilsky, *Hurry Up and Wait: Is Accelerated Approval of New Cancer Drugs in the Best Interests of Cancer Patients?*, Journal of Clinical Oncology, Oct. 2003, at 3718.

drugs while also tending to the needs of desperate patients.[7]

However, recent controversies over the FDA's inability to monitor drug safety have generated a substantial backlash against the agency.[8] Public outrage over the FDA's alleged withholding of safety data regarding antidepressant use by children, the withdrawal of two pain-killers used by millions of Americans, and the withdrawal of an accelerated approval multiple sclerosis drug, have created a perception that the agency is overly susceptible to the influence of the pharmaceutical industry and no longer capable of regulating drug safety in the U.S.[9] After years of successfully pressuring the FDA to adopt more liberal drug approval policies, the cancer community now fears that negative public sentiment will force the agency to revert to a lengthy, cautious framework for evaluating new oncology drugs.[10] Although cancer activists are understandably concerned about the pendulum swinging back to a more conservative agency stance, the FDA and the Oncologic Drugs Advisory Committee (ODAC) do not appear to have embraced a more risk-averse philosophy with regards to oncology products.[11] Instead, the general public backlash against the FDA presents the agency with an excellent opportunity to facilitate improvements to the accelerated approval and fast-track regulations for the benefit of cancer patients.

Section I of this paper is a historical examination of FDA drug approval regulations from the inception of the Federal Food, Drug, and Cosmetic Act of 1938, through the AIDS crisis of the late 1980s and early 1990s,

[7] Id.; see also Carl M. Cannon, *Letter from Washington: Bitter* Pills, Forbes, May 28, 2001, at 21.

[8] See Gorman, supra note 1, at 58.

[9] Id.; see also Anna W. Mathews and John Hechinger, *Are Too Many Unproven Drugs Receiving FDA Early Approval? Process Comes Under Scrutiny*, Wall Street Journal, Mar. 1, 2005, at B1.

[10] Scott Gottlieb, *FDA Moves Cancer Cures Into the Slow Lane*, Forbes Investment Newsletter, Jan. 18, 2005. Available at: http://www.forbes.com/investmentnewsletters/2005/01/18/cz_sg_0118soapbox_inl. html.

[11] FDA Oncologic Drugs Advisory Committee Charter. Available at: http://www.fda.gov/cder/audiences/ acspage/ Oncologiccharter1.htm. The ODAC reviews and evaluates data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of cancer and makes appropriate recommendations to the Commissioner of Food and Drugs. Members of ODAC include authorities on oncology and related professions, an industry representative, and a consumer representative.

to the formalized fast-track and accelerated approval regulations in the FDA Modernization Act of 1997. Section II analyzes the success of the various elements of the fast-track and accelerated approval regulations in expediting important, life-saving drugs to the U.S. market. Section III examines the recent public backlash against the FDA, the growing fears of the cancer community, and the legitimacy of the cancer community's concerns. Section IV takes a brief look at proposed FDA reforms and outlines recommendations for the FDA to improve post-marketing study compliance.

Section I. The Evolution of FDA Drug Approval Regulations

A. History of FDA Drug Approval Authority

Over the course of the FDA's existence, the agency's historically risk-averse perspective has tempered the evolution of policies and regulations regarding the approval of new drugs in the United States. With the inception of the Federal Food, Drug, and Cosmetic Act (FDCA) in 1938, the FDA was built on a solid foundation of consumer protection and a vigilant outlook on new drug approvals.[12] The impetus for the passage of the FDCA was the significant public health catastrophe resulting from the distribution of Elixir of Sulfanilamide; a poisonous drug that caused nearly a hundred deaths after reaching the market without any safety testing.[13] In response to public outcries over the unsafe elixir, the FDCA established the statutory requirement that any new drug would have to receive FDA review prior to entering the marketplace.[14] The

[12]Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. § 301 (1994)).
[13]Beth E. Myers, *The Food and Drug Administration's Experimental Drug Approval System: Is It Good For Your Health?*, 28 Hous. L. Rev. 309, 311-12 (1991). The Elixir of Sulfanilamide was made using the toxic solvent diethylene glycol.
[14]Joel Hoffman, *The Food and Drug Administration's Administrative Procedures*, in Food and Drug Law 16 (Richard M. Cooper ed., 1991).

FDCA empowered the FDA to stop unsafe drugs from reaching the public by requiring a demonstration that a new drug was safe for human consumption.[15] Drug manufacturers were required to submit a new drug application (NDA) for FDA review, and the agency had sixty days to affirmatively respond.[16] However, if the FDA did not respond within the sixty-day time frame, the NDA was considered approved, and the drug manufacturer was allowed to proceed with further development and commercialization.[17] Therefore, even with the passage of the FDCA, there were still opportunities for unsafe drugs to enter the market.

While the FDCA birthed a more cautious process of regulating pre-market drug approvals, the Thalidomide crisis in the early 1960s and the consequent Kefauver-Harris Amendments of 1962 solidified both the FDA's authority and the agency's conservative approach to drug approvals.[18] Because the FDA never approved Thalidomide for use in the U.S., the country was spared from the terrible teratogenic side effects of the pregnancy-related drug.[19] Nevertheless, the thousands of birth defects caused by Thalidomide use in Europe prompted further public demands for an expansion of the FDA's power to protect consumers.[20] The Kefauver-Harris Amendments to the FDCA substantially bolstered the FDA's authority in a number of ways. Pharmaceutical manufacturers were now required to submit "substantial evidence" proving both the effectiveness and safety of a new drug.[21] The new effectiveness requirement established the controlled clinical trial as the standard for developing this empirical proof, and gave the FDA command over the design and structure of clinical trials by demanding specific types of scientific evidence.[22] Additionally, the

[15] Id.
[16] Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 Va. L. Rev. 1753, 1762 (1996).
[17] Richard M. Goodman & Paul D. Rheingold, Lawyer's Drug Handbook 30 (1967).
[18] Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified in scattered sections of 21 U.S.C. § § 301-81 (1994)); see also Merrill, supra note 16, at 1764-65.
[19] Id.
[20] Id.
[21] Patricia I. Carter, *Federal Regulation of Pharmaceuticals in the United States and Canada*, 21 Loy. L.A. Int'l & Comp. L. Rev. 215, 218-19 (1999).
[22] See Greenberg, supra note 2 (1999), at 304; see also Merrill, supra note 16, at 1766.

Kefauver-Harris Amendments extended the FDA's approval timeframe from 60 to 180 days, and in contrast to the FDCA, required affirmative approval by the FDA before a drug could enter the market.[23] These Amendments from 1962 not only gave the FDA ultimate authority over drug approvals, but also established many of the FDA's standard approval processes that exist today.

B. The FDA's Standard New Drug Approval Process

Since the passage of the Kefauver-Harris Amendments, the FDA has enforced a careful, drawn-out, multi-stage drug approval process for most new drugs. The process begins with a drug researcher engaging in pre-clinical testing on animals to determine if a drug is sufficiently safe and promising to risk clinical testing on humans.[24] Most estimates find that pre-clinical testing can last at least thirty months.[25] Following the conclusion of animal testing, the FDA's involvement typically begins when the drug researcher submits an Investigational New Drug Application (IND) to obtain permission to begin human clinical trials.[26] The IND includes disclosure of all active ingredients of the new drug, a review of any previous human experience with the drug, an overview of the entire investigation plan, a list of possible risks and side effects, and a summary of the toxicity and pharmacology results of the animal testing.[27] If the FDA approves the IND, the drug researcher can begin conducting Phase I clinical trials.

[23]See Greenberg, supra note 2, at 303-04 (citing Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 Geo. L.J. 185, 192-95 (1972)).
[24]Charles J. Walsh & Alissa Pyrich, *Rationalizing the Regulation of Prescription Drugs and Medical Devices: Perspectives on Private Certification and Tort Reform*, 48 Rutgers L. Rev. 883, 905 (1996).
[25]Id. at 904-05 & nn.75-78.
[26]21 C.F.R. § 312.23 (2001).
[27]Id.

Phase I clinical trials, which generally last about six months, involve testing of the experimental drug with a group of twenty to eighty volunteers.[28] The main purpose of Phase I testing is to generate safety and pharmacological information of the drug's use in humans.[29] Assuming there are no major toxicities or adverse side effects in Phase I, a drug researcher can proceed with Phase II clinical testing. While Phase I trials are primarily focused on establishing safety data, Phase II trials seek to determine data on efficacy, safety, and short-term tolerability of the drug in small groups of subjects who are inflicted with the disease or condition the new drug is intended to treat.[30] Even though Phase II testing involves controlled trials designed to determine efficacy, the results of the trials may not in and of themselves establish statistically sound proof of effectiveness due to the small number of trial subjects.[31] Other Phase II study objectives include determining the minimum dose that is maximally effective, or that is sufficiently effective without undue toxicity.[32]

If Phase II data produces reasonable evidence of a drug's safety and efficacy, the drug researcher can proceed with arguably the most important clinical trials with Phase III testing. Phase III studies are large-scale, controlled clinical trials typically involving anywhere from a hundred to several thousand subjects.[33] The primary aim of these trials is to confirm efficacy and long-term safety in the administration of the new drug under circumstances closely resembling those under which the drug would be used if approved.[34] In gathering additional information about efficacy and tolerability, the drug researcher seeks to identify the overall risk-benefit relationship of the drug and create an adequate evidentiary basis for dosage and labeling. From a

[28] James T. Gathii, *Rights, Patents, Markets and the Global AIDS Pandemic*, 14 Fla. J. Int'l L. 261, 335 (2002).
[29] Id. Phase I trial volunteers are generally tested for the safe dosage level of the drug, tolerance to the drug, administration of the drug, and how the drug is eliminated from the body.
[30] 21 C.F.R. § 312.21 (1999).
[31] See Greenberg, supra note 2, at 305.
[32] Id.
[33] *From Test Tube to Patient: New Drug Development in the United States*, FDA Consumer, Nov. 1987, at 12-15.
[34] See Gathii, supra note 28, at 336.

pharmaceutical company's perspective, success in Phase III trials produces safety and efficacy data required to fulfill statutory and regulatory obligations for approval and commercialization.[35] Following the completion of all necessary clinical trials, a pharmaceutical company can enter the pre-registration period and submit a NDA to the FDA seeking marketing approval for the new drug.[36] Submitting a NDA requires a great deal of information, including all the data collected during the pre-clinical and clinical phases establishing safety and efficacy, the complete ingredients of the drug, the composition of the drug, a description of the manufacturing, processing, and packaging methods, and samples of the drug and its proposed label.[37] The NDA approval process can take anywhere from several months to a few years before the FDA decides to allow a new drug to enter the marketplace.[38]

The standard pre-approval process is a lengthy and expensive endeavor that reflects the risk-averse, consumer protection origins of the FDCA and the Kefauver-Harris Amendments. The average time it takes for a new drug to go through the three phases of clinical testing is approximately five years, but can range anywhere from two to ten years.[39] A Tufts University Center for the Study of Drug Development (CSDD) report finds that on average, the time between starting research on a new drug and ultimately receiving FDA approval ranges between ten and fifteen years, and that during that timeframe, a pharmaceutical developer spends on average $802 million.[40] Following approval, the FDA can add further burdens to a pharmaceutical company by conditioning approval on the success of Phase IV post-marketing studies.[41] Based on those studies, the

[35]See Greenberg, supra note 2, at 305.
[36]See Walsh & Pyrich, supra note 24, at 905 n.79.
[37]Id. at 908; see also 21 C.F.R. § § 314.50-.90 (2001).
[38]Melissa M. Bean, *Fatal Flaws In the Food and Drug Administration's Drug-Approval Formula*, 2003 Utah L. Rev. 881, 885-86 (2003).
[39]See Walsh & Pyrich, supra note 24, at 905 n.79
[40]Tufts University Center for the Study of Drug Development, *BACKGROUNDER: How New Drugs Move through the Development and Approval Process*, Nov. 1, 2001. Available at: http://csdd.tufts.edu/ NewsEvents/RecentNews.asp?newsid=4.
[41]See Walsh & Pyrich, supra note 24, at 914 n.126.

FDA may withdraw its approval if a drug seems unsafe, ineffective or if safer alternatives enter the market.[42] As a result of this diligent and complex process the FDA has been perceived as one of the safest and most effective regulatory agencies, but also one that may be too risk-averse and slow.[43]

C. AIDS and Expanded Access

Even before the emergence of the AIDS epidemic, critics of the FDA approval process were outspoken in their condemnation of the agency for being too conservative in approving drugs used to treat life-threatening diseases.[44] Michael Greenberg, in his analysis of the FDA's new drug screening process prior to and after the AIDS epidemic, highlights the cancer therapy Laetrile as a prime example of the tensions between the FDA's restrictive policy and the autonomy of desperate patients.[45] During the 1970s, many cancer patients believed Laetrile, a drug with no controlled efficacy data, was an effective cancer therapy.[46] Despite ample protest by cancer patients and Laetrile advocates, the FDA refused to approve the drug without any clinical trial data supporting safety and effectiveness.[47] Undeterred, a group of cancer patients brought suit against the FDA to enjoin the agency's interference in the interstate trade of the drug.[48] Unfortunately, the U.S. Supreme Court ultimately upheld the FDA's authority and refused to make an exception to FDA approval requirements for drugs used to treat terminally ill conditions.[49] However, while the FDA remained adamant in enforcing its restrictive approval regulations, the agency did begin to recognize a need to expedite the

[42]Id. at 914 n.125 (citing 21 U.S.C. § 355(e) (1994)).
[43]See Bean, supra note 38, at 883; see also Cray, supra note 2, at 109.
[44]Id; see also Greenberg, supra note 2, at 306-07.
[45]Id.
[46]Peter Barton Hutt & Richard A. Merrill, Food and Drug Law: Cases and Materials 557-59 (2d ed. 1991).
[47]Id.
[48]United States v. Rutherford, 442 U.S. 544 (1979); see also Kathryn A. Piffat, *Liability for Injuries Caused by Unapproved Pharmaceuticals Marketed to U.S. Consumers Abroad*, 7 B.U. Int'l L.J. 155, 167-71 (1989).
[49]Id.

availability of drugs for terminally ill patients with little to no alternative treatments.

In 1977, the FDA attempted to expand access to critical, life-saving drugs by implementing a compassionate use IND.[50] Although the FDA never formalized the compassionate use IND through administrative rule-making, the informal exemption permitted physicians to prescribe an experimental drug to a patient with a severe illness even if it was not for the purpose of clinical investigation.[51] While the compassionate use IND offered new hope to those with life-threatening diseases, several barriers prevented the widespread use of the exemption. First, the compassionate use IND was only offered on a case-by-case basis and required significant time and effort from a patient's physician to petition the FDA.[52] Second, even if a physician went through the bureaucratic hurdles to submit a compassionate use IND, there was no guarantee the FDA would approve the exemption.[53] Third, even with FDA approval to the exemption, drug companies were wary of participating because they were required to provide the experimental treatment free of charge.[54] As a result, the FDA's initial attempt at expanding access and moving away from its conservative stance was mostly deemed a failure.[55]

Another piecemeal attempt at allowing greater access to life-saving drugs was the FDA's introduction of the

[50]Ken Flieger, *FDA Finds New Ways to Speed Treatments to Patients*, FDA Consumer Magazine, Oct. 1993.

[51]Id.; see also Frank E. Young, John S. Norris, Joseph A. Levitt, & Stuart L. Nightingale, *The FDA's New Procedures for the Use of Investigation Drugs for Treatment*, Journal of the American Medical Association, Apr. 15, 1998, at 2267. The FDA has a long history of informally approving compassionate use INDs for individuals with life-threatening conditions who are ineligible for ongoing clinical trials and unresponsive to existing treatments. The FDA also has an emergency IND provision that allows the distribution of a drug for a specific use prior to filing of an IND.

[52]Peter S. Arno & Karyn L. Feiden, Against the Odds: The Story of AIDS Drug Development, Politics and Profits 34-35 (1992).

[53]Id.

[54]Lisa Terrizzi, *The Need for Improved Access to Experimental Drug Therapy: AIDS Activists and Their Call for a Parallel Track Policy*, 4 Admin. L.J. 589, 600-01 n.62 (1991).

[55]See Flieger, supra note 50; see also Greenberg, supra note 2, at 316.

personal use import exemption in 1989.[56] The exemption allows individuals in the U.S. to import limited quantities of unapproved drugs for their personal use.[57] While the program was originally intended for AIDS and cancer patients, it currently covers many different drugs.[58] Although the exemption helped remedy situations for patients who could afford expensive imported drugs, critics complained that the program favored the wealthy, created greater potential for the exploitation of the seriously ill, and provided a disincentive for terminally ill patients to participate in clinical trials for potentially effective drugs.[59] The personal use import exemption did provide seriously ill patients expanded access to unapproved medicines, but it did nothing to hasten the approval of life-saving therapies in the United States.

Compassionate use INDs and the personal import use exemption were important first efforts to expand access, but did little to change the FDA's slow, cumbersome approval processes. Major changes to the FDA's drug approval regulations did not occur until the onset of the AIDS epidemic of the 1980s. Compared to patients afflicted with other conditions, the first AIDS patients faced imminent death from a mysterious new disease and had an almost complete lack of treatment options.[60] This desperation forced AIDS patients to resort to self-treatment using untested and unapproved drugs, and a powerful and vocal activist community mounted escalating pressure on the FDA to reform the drug approval process to speed the development and distribution of AIDS therapies.[61] In conjunction with a strong community of cancer activists, AIDS

[56]Audrey A. Hale, *The FDA's Mail Import Policy: A Questionable Response to the AIDS Epidemic*, 16 Rutgers Computer & Tech. L.J. 169, 180-94 (1990).
[57]Id. at 180-81.
[58]Id. at 169-170, 180.
[59]See Greenberg, supra note 2, at 316-17; see also Myers, supra note 13, at 309-10.
[60]See Greenberg, supra note 2, at 311.
[61]Philip J. Hilts, *How the AIDS Crisis Made Regulators Speed Up*, N.Y. Times, Sept. 24, 1989, at D5; see also David Kessler, IOM 25th Anniversary Lecture, Seattle, WA, Nov. 7, 1994. Available at: http://www.fda.gov/bbs/topics/SPEECH/SPE00056.htm. Kessler, a former FDA commissioner noted that "AIDS activists were literally scaling the walls of the FDA building...demanding access to potential therapies that had barely moved out of the test tube."

activists were the primary drivers behind a slew of reforms to the FDA's approval processes from the late 1980s through the 1990s.[62]

The first significant FDA response to pressure from the AIDS community came in 1987 with the introduction of the treatment IND.[63] The treatment IND was an expansion and formal codification of the compassionate use IND, and it attempted to rectify some of the problems that led to the failure of its predecessor. Rather than being applied on a case-by-case basis, treatment INDs permit a promising experimental treatment to be provided to a population of seriously ill patients while concurrent research and testing of the drug is conducted under the standard FDA approval process.[64] In addressing the commercial disincentive to provide experimental drugs for free, treatment INDs allow drug companies to petition the FDA for authorization to charge patients for experimental treatments.[65] Although this raises the potential for drug companies to abuse patients by charging extremely high prices, the FDA's decision-making power over the petition allows the agency to create some commercial incentive while simultaneously checking possible extortion.[66] In terms of who can apply for the exemption, the FDA assumed drug companies would be the primary drivers of submitting treatment IND requests, but the exemption also allows physicians to apply for a treatment IND when a drug company has yet to do so.[67]

[62]Id.; see also Julie Rovner, *FDA Speeds Up Some Approval Procedures*, 347 Lancet 1038 (1996).

[63]See 21 C.F.R. § 312.34 (1999); see also Ellen C. Cooper, *Changes in Normal Drug Approval Process in Response to the AIDS Crisis*, 45 Food Drug Cosm. L.J. 329, 333 (1990).

[64]Id. Treatment INDs become available when the experimental drug is intended to treat a serious or life-threatening disease, there are no satisfactory treatment alternatives for the target disease and patient population, the drug is already being researched through controlled trials pursuant to an IND or has completed that research, and the sponsor of the IND is pursuing marketing approval for the experimental drug with due diligence.

[65]See 21 C.F.R. § 312.7(d)(2) (1999).

[66]See Greenberg, supra note 2, at 320; see also Shulman and Brown, supra note 5, at 505. Companies can bill patients to recover the costs of a distributed treatment IND drug, but the amount cannot exceed the manufacturing, research and development, and distribution costs.

[67]See 21 C.F.R. § 312.35 (1999). The FDA also had considerable freedom to deem a treatment IND as submitted whenever it found it to be appropriate.

Despite the improvements over the compassionate use IND, the treatment IND has endured criticism by activists that the exception does too little in getting experimental drugs to desperate patients.[68] The FDA still wields a great degree of authority in determining when treatment IND drugs can become available, and generally, the regulations make it difficult for experimental drugs to be distributed prior to entering Phase III trials.[69] In order for an experimental drug to be available prior to Phase III trials, the FDA must determine that the drug could be reasonably effective in treating an "immediately life-threatening" condition without significant risks of harm to patients.[70] Experimental drugs that merely treat "serious" conditions are generally unavailable until Phase III trials, assuming all other treatment IND requirements are met.[71] Because experimental drugs can at best become available in Phase II, and most drugs are not likely to be available until Phase III, treatment INDs only marginally expand access of life-saving therapies to market.[72] Combined with the concerns regarding payment and reimbursement for the experimental drugs, the minimal acceleration provided by treatment INDs was insufficient to quell the voices of AIDS activists.[73]

Five years after the introduction of treatment INDs, the FDA sought to expand early availability of experimental AIDS treatments through the parallel track initiative.[74] Going beyond the parameters of treatment

[68]See Arno & Feiden, supra note 52, at 101-02.

[69]See 21 C.F.R. § 312.34 (1999).

[70]See id. (defining immediately life-threatening as stage of disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.).

[71]See id. (noting that "serious" was not defined under the regulation, providing the FDA with considerable latitude in evaluating treatment INDs for "serious" conditions).

[72]See Terrizzi, supra note 54, at 608-10. See also Shulman and Brown, supra note 5, at 507-09. Excluding treatment IND drugs that received accelerated approval, treatment IND drugs in fact had a longer regulatory phase than non-treatment INDs from 1987-1994. Perhaps treatment IND drugs are inherently more likely to receive accelerated approval, and they appeared to have shorter FDA review times due to increased data accumulation and earlier FDA involvement, but the ultimate effect of treatment INDs on accelerating marketing approval is inconclusive.

[73]See Arno & Feiden, supra note 52, at 101-02.

[74]Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People with AIDS and other HIV-Related Disease, 57 Fed. Reg. 13,250 (1992).

INDs, the parallel track program makes experimental AIDS drugs available "when the evidence for effectiveness is less than generally required for a treatment IND," which can be as early as the end of Phase I, provided that Phase II trials have begun enrollment.[75] The parallel track initiative is exclusively designed for drugs treating AIDS or HIV-related conditions, and is aimed towards expanding access to patients who are unable to participate in ongoing clinical trials.[76] In balancing the lower level of required safety and efficacy evidence, parallel track requires all physicians to file safety reports and features enhanced oversight by the National Institutes of Health AIDS Research Advisory Committee.[77]

With the advent of other FDA procedures for expanding and expediting drug development, the parallel track initiative has gone from minimally used to nearly obsolete.[78] The higher risk level assumed by patients of parallel track drugs and wariness by sponsors over financial issues in providing the drugs led to the infrequent use of the initiative.[79] Drug companies are allowed to charge for parallel track drugs, but they must obtain prior authorization from the FDA, further exacerbating similar financial worries associated with treatment INDs.[80] If a drug company cannot obtain reimbursement for a parallel track drug, then the large number of potential patients and necessary levels of inventories of the drug create legitimate cost concerns for any sponsor. As a result, only one experimental AIDS drug has been made available using the parallel track initiative.[81]

[75] Id. at 13,256; see also Shulman and Brown, supra note 5, at 509.

[76] Id.

[77] Id. Data gathered from parallel track studies can be used to corroborate clinical trial data, but because parallel track drugs are not used in controlled trials, the supporting data is mostly useful for confirming safety.

[78] See Greenberg, supra note 2, at 327.

[79] Id. at 325-27.

[80] 21 C.F.R. § 312.7(d)(1). The sponsor must show why the trial or distribution cannot proceed without charging patients for the drug. The sponsor cannot charge an amount greater than the manufacturing, research and development, and distribution costs of the drug.

[81] See Greenberg, supra note 2, at 327.

D. Expediting Drug Approvals

Even though treatment INDs and the parallel track initiative did little to ultimately expedite drug approvals, their inception showed the FDA's willingness to soften its conservative stance and adjust risk-benefit analyses based on specific, seriously ill patient groups. Starting in the early 1990s, the FDA made substantial efforts to get new drugs to market faster. These new, codified regulations represented significant achievements after years of political pressure from AIDS and cancer activists, and they were partially based on regulatory innovations used in the mid 1980s to speed the approval of the AIDS drug azidothymidine (AZT).[82]

The expedited development regulations, commonly known as the "Subpart E" regulations, represent several established FDA processes that were finally codified in 1992.[83] The goal of the Subpart E regulations is to accelerate the development and approval of drugs used to treat life-threatening and severely debilitating diseases.[84] From a technical standpoint, the acceleration through the development stage is accomplished through a more collaborative arrangement between the drug researcher and the FDA.[85] By applying the "coherent whole" model used in approving AZT, the regulations embrace a policy where "interventions at one stage are designed to lead to efficiencies in the next."[86] As a result, the Subpart E framework features early and frequent consultations between the drug researcher and the FDA in the design of clinical trials in order to ensure that the outcomes will be useful in meeting subsequent approval requirements.[87] In addition

[82]See Arno & Feiden, supra note 52, at 41-46

[83]Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended To Treat Life-Threatening and Severely Debilitating Illnesses, 53 Fed. Reg. 41,516, 41,523 (1998); see also 21 C.F.R. § 312.80 (1999).

[84]Id.

[85]21 C.F.R. § 312.82 (1999) (early consultation between drug researchers and the FDA); 21 C.F.R. § 312.87 (1999) (ongoing FDA monitoring of clinical trials).

[86]Shulman and Brown, supra note 5, at 511 (citing 53 Fed. Reg. at 41,516).

[87]See 21 C.F.R. § 312.82 and 21 C.F.R. § 312.87.

to ongoing monitoring of clinical trials by the FDA, a drug researcher can request a conference with the FDA at the end of Phase I to effectively design an expanded, multi-center Phase II study.[88] Based on the success of the expanded Phase II study, the regulations allow a drug company the opportunity to forego Phase III trials and submit a NDA at the end of Phase II.[89] The regulations also authorize post-marketing studies, or Phase IV studies, which allow promising experimental drugs to reach the market faster and then continue confirmatory research after approval.[90]

In addition to the procedural efficiencies introduced by the regulations, Subpart E drugs are evaluated with a modified risk-benefit analysis. First, the regulations specifically include the severity of the disease and lack of alternative treatments in the FDA's evaluation of a Subpart E drug's approval.[91] Second, in recognizing the higher risk tolerance of desperate, seriously ill patients, the regulations adopt a more flexible application of the FDA's conservative safety and effectiveness standards.[92] This modified risk-benefit evaluation coupled with intensive collaboration between drug researchers and the FDA significantly shortened the time to market for life-saving drugs which qualified under Subpart E regulations.[93]

The same year as the Subpart E regulations were codified, the FDA substantially shortened approval review times for all drugs by implementing the Prescription Drug User Fee Act of 1992 (PDUFA).[94] In responding to constant criticism about the slow, cumbersome drug approval process, the FDA frequently claimed that

[88]Id.; see also Shulman and Brown, supra note 5, at 512.
[89]Id.
[90]21 C.F.R. § 312.85 (1999).
[91]See 21 C.F.R. § 312.80.
[92]Id.
[93]See Shulman & Brown, supra note 5, at 513-14. In an analysis of the 28 Subpart E approvals between 1988 and 1994, Subpart E drugs had a shorter average total development time of 7.5 years.
[94]Prescription Drug User Fee Act, Pub. L. No. 102-571, § 101, 106 Stat. 4491 (1992).

reviewing NDAs took an extended period of time due to the agency's budget constraints and the inability to hire more reviewers.[95] The PDUFA sought to address this concern by levying fees on pharmaceutical companies to finance the hiring of additional reviewers.[96] Under the PDUFA, the FDA can collect user fees from drug companies who file NDAs, companies who market approved prescription drugs, and owners of retail prescription drug stores.[97] While the PDUFA has raised questions about the financial relationship between pharmaceutical companies and the agency that regulates them, the Act has allowed the FDA to substantially increase its workforce and reduce the agency's review times.[98] The PDUFA was only authorized for five years, but was subsequently extended under the FDA Modernization Act in 1997.[99]

In 1993, the FDA formally enacted perhaps the most significant initiative to expedite drug approvals, the accelerated approval, or Subpart H regulations.[100] While Subparts E and H are both directed at drugs that address similar conditions, accelerated approval is markedly different in the standards used to evaluate an experimental drug's NDA.[101] The FDA standard for regulatory approval is typically convincing evidence of a clinical benefit (i.e. prolonged survival or increased quality of life) in a controlled Phase III trial.[102] Accelerated approval standards radically depart from the traditional evidentiary standards and provisional approval can be granted based on evidence of a surrogate measure of clinical benefit (i.e. tumor shrinkage) in a single, uncontrolled clinical trial.[103] In order for an experimental drug to be approved based on a surrogate

[95]See Merrill, supra note 16, at 1798.
[96]John Henkel, *User Fees To Fund Faster Reviews*, FDA Consumer, Oct. 1993, at 19.
[97]See Prescription Drug User Fee Act § 736, 106 Stat. at 4494-6.
[98]See Bean, supra note 38, at 910; see also Parver, supra note 4, at 1264-65; Julie Rovner, *Once Controversial U.S. FDA-Overhaul Bill Advances*, 350 Lancet 1153, 1153 (1997); Jocelyn Kaiser, *Regulatory Agencies: FDA Reform Starts Down the Track*, Science, Mar. 1, 1996, at 1228.
[99]FDA Modernization Act, Pub. L. No. 105-115, § 101, 111 Stat. 2296, 2296-2305.
[100]21 C.F.R. § 314.500 (1999) (accelerated approval of drugs); 21 C.F.R. § 601.4 (1999) (accelerated approval of biologics).
[101]Id.; Subpart E regulations refer to life-threatening and severely debilitating illnesses, 21 C.F.R. § 312.80, while accelerated approval regulations refer to serious or immediately life-threatening illnesses 21 C.F.R. § § 314.500, 601.40.
[102]See Roberts and Chabner, supra note 6 at 502.
[103]Id.; see also David M. Cocchetto and Douglas R. Jones, *Faster Access to Drugs for Serious or Life-Threatening Illnesses Through Use of the Accelerated Approval Regulation in the United States*, Drug Information Journal, Feb. 15, 1998, at 29. In

endpoint, the surrogate measure must be reasonably predictive of a clinical benefit and the drug must offer a meaningful therapeutic benefit over existing alternative treatments.[104] For accelerated approval, a drug company is not required to show a direct, validated link between the surrogate measure and clinical benefit, and in fact, if that link is already firmly established, then the drug may have to be evaluated under standard procedures or Subpart E.[105] Because of the uncertainty associated with surrogate endpoints, accelerated approval is granted conditionally, and the drug manufacturer must conduct confirmatory Phase IV trials following approval.[106] Generally, the FDA expects that these confirmatory studies will be underway at the time of accelerated approval, but this is not a requirement.[107] Based on the results of the Phase IV trials, the FDA can choose to withdraw the drug from the market.[108] By approving drugs based on intermediate, but predictive endpoints, and mandating confirmatory research after approval, the FDA can use the Subpart H regulations to substantially shorten pre-approval development and review times.

E. The FDA Modernization Act and the Fast-Track Programs

The FDA Modernization Act of 1997 (FDAMA) was a comprehensive statute aimed at reforming a multitude of processes within the FDA.[109] Among the changes brought on by the FDAMA, the provisions that codified

March 1996, President Clinton announced an initiative entitled "Reinventing the Regulation of Cancer Drugs" which led the FDA to expand use of accelerated approval processes for cancer treatments by basing approvals on surrogate endpoints like tumor shrinkage instead of more traditional endpoints.

[104]See Shulman and Brown, supra note 5, at 514.

[105]Id.

[106]Id. at 514-15. The FDA can also add further conditions to accelerated approval in order to compensate for safety and efficacy concerns, including restricted distribution, advance review of advertising, and a streamlined procedure withdrawal of the drug.

[107]Ramzi Dagher et al., *Accelerated Approval of Oncology Products: A Decade of Experience*, Journal of the National Cancer Institute, Oct. 20, 2004, at 1500.

[108]Id.

[109]FDA Modernization Act § 101, 111 Stat. at 2296; see also Parver, supra note 4, at 1249. The FDAMA covers foods, drugs, and medical devices, and has generic provisions that apply to all parts of the FDA. Additionally, the FDAMA includes regulations on the research, manufacturing, and marketing of new drugs, including authorization to market off-label uses for drugs.

and expanded the incremental reforms of the late 1980s and early 1990s truly demonstrated the FDA's desire to adapt and react to legitimate public health issues and political pressure. At a policy level, one goal of the FDAMA was to improve the "historically adversarial relationship between pharmaceutical companies and the FDA."[110] By reinstating the PDUFA's user fee scheme as well as improving mechanisms for interactions between pharmaceutical companies and agency officials at a variety of levels, the FDAMA creates a more cooperative environment that raises the potential for speedier drug development and approval.[111]

In terms of expediting drug approvals, the most significant aspect of the FDAMA was the consolidation and codification of a variety of incremental approval reforms into a comprehensive fast-track development program.[112] The fast-track program is designed to facilitate clinical development and expedite review of new drug or biological products intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet needs for new therapy.[113] A pharmaceutical company can apply for fast-track designation for any product, but the product and the specific indication for which it is being studied must meet the qualifying "life-threatening" and "unmet need" criteria. Pharmaceutical companies can begin discussing fast-track designation with the FDA as early as the pre-IND meeting, and the designation can be applied when an IND is submitted.[114] The FDA attempts to respond to fast-track designation requests

[110]Steven R. Salbu, *The FDA and Public Access to New Drugs: Appropriate Levels of Scrutiny in the Wake of HIV, AIDS, and the Diet Drug Debacle*, 79 B.U. L. Rev. 93, 121 (1999).

[111]See FDA Modernization Act § § 101-07, 111 Stat. at 2298-2305; see also Parver, supra note 4, at 1259-1261. The FDA established meeting management goals to ensure prompt scheduling and responses, major dispute resolution procedures with shorter deadlines, technology enhancements, and other improvements designed to improve the interaction between the FDA and pharmaceutical companies.

[112]See Milne and Bergman, supra note 5, at 71-72. Prior to the passage of the FDAMA, "fast-track" meant many things to many people, including Subpart E, Subpart H, rolling NDAs, "priority" status under the PDUFA, and even treatment INDs and parallel track. The FDA has explicitly said expanded access programs such as treatment INDs are distinct from the fast-track program.

[113]FDA Guidance for Industry, Fast Track Drug Development Programs - Designation, Development, and Application Review, Procedural Revision 1, July 2004. Available at http://www.fda.gov/cder/guidance/ 5645fnl.htm (hereinafter Fast-Track guidance).

[114]Id. at 8.

within sixty days of submission.[115]

Much like the procedural goals of the Subpart E regulations, the fast-track program seeks to facilitate clinical development in a variety of ways. First, fast-track regulations provide for early and regular consultations between the FDA and the new drug's sponsor; especially at key points in the clinical developments process such as pre-IND, end of Phase I, end of Phase II, pre-NDA, and early in the labeling process.[116] Second, the fast-track guidelines specifically outline the sponsor's responsibility of providing important written correspondence to the FDA, and also the FDA's responsibility to deliver timely comments on the design of the principle controlled clinical trials and the sufficiency of the sponsor's Phase II and III development plans.[117] Third, fast-track sponsors have formal dispute resolution and escalation procedures to appeal FDA decisions falling under the fast-track program.[118] The formalized procedural mechanisms that come with fast-track designation attempt to reduce clinical development time by introducing early cooperation, enhanced predictability of FDA decision-making, and efficient agency interventions.

The fast-track program offers two procedures that can significantly reduce the time it takes for the FDA to evaluate a NDA. Fast-track designation does not guarantee any of these review-expediting procedures, but based on the medical need for fast-track products, they are likely to be considered for at least one of them.[119] First, fast-track designation means that the product "ordinarily will be eligible for priority review."[120] A "standard" NDA review sets the target date for completing all aspects of the review and the FDA's approval decision at ten months after the date the NDA is filed.[121] A "priority" review sets the target date for an

[115]Id. at 9.
[116]Id. at 10-11.
[117]Id. at 11-12
[118]Id. at 15.
[119]See Roberts & Chabner, supra note 6, at 502.
[120]Id.
[121]Center for Drug Evaluation and Research Manual of Policies and Procedures, MaPP 6020.3, Priority Review Policy, April 22, 1996; Center for Biologics Evaluation and Research Manual of Standard Operating Procedures and Policies, SOPP 8405, Complete Review and Issuance of Action Letters, June 11, 1998.

FDA decision at six months.[122] Second, the fast-track program allows for a "rolling review" of portions of a NDA before the full application is submitted.[123] The FDA can then review the NDA as the completed sections are submitted rather than waiting until the entire application arrives for evaluation. In terms of expediting clinical development and review time, fast-track products can also be considered for accelerated approval under the previously enacted Subpart H regulations.[124]

The FDAMA formally established the three main procedures currently used to expedite drugs to market. Fast-track designation is a formal mechanism of interaction between a drug company and the FDA that reduces inefficiencies in clinical development and NDA review. Priority review offers the benefit of a four-month reduction of the time it takes for the FDA to evaluate a NDA. Accelerated approval primarily deals with the design and content of the studies used to support a marketing claim and can significantly speed a drug to market using surrogate endpoints for conditional approval. Fast-track designation does not necessarily lead to a priority review or accelerated approval, and an applicant can apply to use any element of the fast-track programs without receiving fast-track designation.[125] The FDA is currently conducting its own pilot programs with fast-track designated products to assess the added value, costs, and impact of more extensive feedback during drug development and rolling review of NDAs.[126]

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[122]Id.

[123]Fast-Track Guidance, supra note 113, at 12-14. The FDA will allow a "rolling review" if (1) the clinical trials that would form the basis for the FDA's determination of the safety and effectiveness of the product and that would support drug labeling are nearing completion or have been completed, (2) the FDA agrees that the product continues to meet the criteria for fast track designation, and (3) the FDA agrees that preliminary evaluation of the clinical data supports a determination that the product may be effective.

[124]Id. at 14-15.

[125]Center for Drug Evaluation and Research, "Fast Track, Priority Review and Accelerated Approval", updated Apr. 26, 2005. Available at http://www.accessdata.fda.gov/scripts/cder/onctools/Accel.cfm (hereinafter Oncology Tools Expedited Products).

[126]Draft Guidance for Industry Continuous Marketing Applications: Pilot 1 – Reviewable Units for Fast Track Products Under PDUFA, June 2003, available at http://www.fda.gov/cder/guidance/5207dft.pdf; Draft Guidance for Industry Continuous Marketing Applications: Pilot 2 – Scientific Feedback and Interactions During Development of Fast Track Products Under PDUFA, June 2003, available at http://www.fda.gov/cder/guidance/5208dft.pdf.

Section II. Analyzing the Success of Accelerated Approvals and Fast-Track

During the past decade and a half, the FDA reformed drug approval processes to allow faster introductions of drugs primarily for desperate patients with life-threatening diseases. Accelerated approval and the fast-track program are the most commonly used mechanisms to expedite drugs to market, and both procedures have likely saved or improved countless lives.[127] However, while accelerated approval gained immediate praise for reducing time to market for important new therapies, the pharmaceutical industry and the FDA have yet to fully quantify and recognize the benefits of the fast-track program.[128] The early acceptance of accelerated approval was based on the seemingly obvious advantages of using surrogate endpoints to significantly reduce clinical development timeframes.[129]

A. Accelerated Approval

The first analysis of accelerated approvals, published two years after the formal implementation of Subpart H, clearly demonstrated the virtue of the program.[130] By the end of 1994, eight drugs and supplemental applications had received accelerated approval under Subpart H (3 new chemical entities, 2 biotechnology products, and 3 efficacy supplements for already approved drugs), with five of the approvals intended for the treatment of AIDS and HIV-related diseases.[131] On average, the clinical development time for the five newly

[127] See Tufts CSDD Fast-Track Study, supra note 5, at 2.
[128] See Milne and Bergman, supra note 5, at 72-73; see also Shulman and Brown, supra note 5, at 516.
[129] Id.
[130] Id.
[131] Id.; see also FDA New Drug Approval Report "NDA Approvals Under Subpart H", updated Mar. 31, 2005 (hereinafter "Accelerated Approvals - NDAs"). Available at: http://www.fda.gov/cder/rdmt/ accappr.htm; FDA New Drug Approval Report "NDA Supplements Approved Under Subpart H", updated Mar. 31, 2005 (hereinafter "Accelerated Approvals – NDA Supplements"). Available at: http://www.fda.gov/cder/rdmt/accappr1.htm; FDA New Drug Approval Report "Biological

approved drugs was 4.2 years; a substantial decrease from the average ten to fifteen year clinical development time for most other new drugs.[132] Additionally, the average FDA review period for all eight Subpart H approvals was 9.1 months, with an average 8.4 months of review time for the five newly approved drugs.[133] Compared to standard median FDA review times in 1993 and 1994 of nearly two years, the review process for Subpart H drugs was truly accelerated.[134] Another study examining accelerated approvals between 1992 and 1997 showed that the Subpart H regulations enabled twenty drugs to reach patients at least one or two years earlier than would have been possible otherwise.[135] Although Subpart H regulations were primarily intended for AIDS treatments, products receiving accelerated approval in the early years of the regulations also included cancer treatments (especially after the Cancer Drug Initiative of 1996), as well as drugs for multiple sclerosis, cystic fibrosis, and mycobacterial infections.[136]

The success of the accelerated approval regulations has continued since its codification in early 1993. Since then, the FDA has granted accelerated approval to over sixty distinct drugs or biologics.[137] Of the eighteen drugs approved to treat patients infected with HIV, sixteen of them were expedited to market under Subpart H.[138] The average review time for these AIDS treatments was less than six months.[139] Since the first cancer

Products Approved Under Subpart E", updated Mar. 31, 2005 (hereinafter "Accelerated Approvals – Biologics"). Available at http://www.fda.gov/cder/rdmt/BIOAPPR.htm.

[132]See Shulman and Brown, supra note 5, at 515; see also Tufts University Center for the Study of Drug Development, supra note 5, at 1.

[133]See Shulman and Brown, supra note 5, at 515.

[134]See FDA New Drug Approval Report "CDER Approval Times for Priority and Standard NMEs and New BLAs Calendar Years 1993 – 2004", updated Mar. 22, 2005 (hereinafter "NME/New BLA Approval Times"). Available at: http://www.fda.gov/cder/rdmt/NMEapps93-04.htm; FDA New Drug Approval Report "Approval Times for Priority and Standard NDAs and BLAs Calendar Years 1993 – 2004", updated Mar. 22, 2005 (hereinafter "NDA/BLA Approval Times"). Available at: http://www.fda.gov/cder/rdmt/ NDAapps93-04.htm. In 1993, median approval time for a new molecular entity (NME)/new biologic was 14.9 months for priority designations and 27.2 months for standard designations; median approval time for a NDA/BLA was 20.5 months priority designations and 26.9 months for standard designations. In 1994, median approval time for a new molecular entity (NME)/new biologic was 14.0 months for priority designations and 23.7 months for standard designations; median approval time for a NDA/BLA was 14.0 months priority designations and 21.0 months for standard designations.

[135]See Cocchetto and Jones, supra note 103, at 34.

[136]Id. at 29; see also Shulman and Brown, supra note 5, at 515.

[137]Calculations based on data from Accelerated Approvals – NDAs, Accelerated Approvals – NDA Supplements, and Accelerated Approvals – Biologics, supra note 131. FDA Approval Reports indicate 87 accelerated approvals of NDAs, NDA Supplements, BLAs, and BLA Supplements through March 2005. Of the 87 accelerated approvals, 60 distinct drugs or biologics are represented.

[138]See Roberts and Chabner, supra note 6, at 502.

[139]Id.

drug was granted accelerated approval in 1995, nearly a third of all approved cancer treatments have entered the market via accelerated approval, with a median total development time 5.5 years shorter than cancer drugs approved through standard mechanisms.[140] On average, FDA review times for all drugs, biologics, and supplemental applications under Subpart H have remained below nine months.[141] In 2004, the median approval time for an accelerated approval was approximately six months, while median approvals for standard designated drugs and biologics ranged between 13 and 25 months.[142] Some new drugs and supplemental applications have even been approved under Subpart H in a matter of weeks.[143] Over the past twelve years, accelerated approvals have expanded beyond AIDS and cancer to account for treatments for a wide range of diseases including hypertension, tuberculosis, and anthrax infection.[144] Based on the reduction in clinical development and approval times, the FDA appears to have reached its goals in enacting the accelerated approval regulations. However, as seen in Section III of this paper, the Subpart H regulations have not been without controversy.

B. Fast-Track Programs

Unlike accelerated approval, the fast-track program encountered early skepticism from the pharmaceutical

[140]Id.; see also Steven Hirschfeld et.al., Food and Drug Administration (FDA) Experience With the Accelerated Approval program for Oncology Products, Proc. Am. Soc. Clin. Oncol., Jun. 2003, at 520. Presentation available at: http://media.asco.org/asco/meetings_education/vm/2003/slides_only/ slide.asp?id=3303&max=20.

[141]Calculations based on data from Accelerated Approvals – NDAs, Accelerated Approvals – NDA Supplements, and Accelerated Approvals – Biologics, supra note 131. Average approval time for NDAs under Subpart H was 8.9 months. Average approval time for NDA Supplements under Subpart H was 6.1 months. Average approval time for BLAs and BLA Supplements under Subpart H was 13.2 months.

[142]Calculations based on data from Accelerated Approvals – NDAs, Accelerated Approvals – NDA Supplements, and Accelerated Approvals – Biologics, supra note 131, and NME/New BLA Approval Times, NDA/BLA Approval Times, supra note 134.

[143]Id. For example, the NDA for Crixivan, an AIDS therapy, was approved in six weeks, a NDA supplement for Gleevec to treat pediatric leukemia was approved in four weeks, and a NDA supplement for Levaquin as an oral solution to treat anthrax was approved in two weeks.

[144]See Accelerated Approvals – NDAs, Accelerated Approvals – NDA Supplements, and Accelerated Approvals – Biologics, supra note 131.

industry and an undercurrent of doubt within the FDA. Despite earlier studies that demonstrated that pre-IND meetings and end of Phase II meetings reduced clinical development time, the pharmaceutical industry had trouble recognizing the value of the fast-track program over existing regulatory mechanisms and found the program "soft and really not well-defined."[145] Other industry specialists were wary of added bureaucracy when they already had close working relationships with the FDA.[146] Critics feared that fast-track designation was merely a public relations device to showcase exciting new products, raise the hopes of desperate patient populations, and boost the stock prices of small biotechnology companies who were financially reliant on a single fast-track product.[147] Even within the FDA, senior officials questioned how the formalized fast-track program would actually change how drugs were developed and evaluated from an agency standpoint because many of the fast-track mechanisms were already in use prior to the passage of the FDAMA.[148] The benefits of improved approval mechanisms such as "rolling review" were tempered with FDA guidance that actual review may not commence until the agency's receipt of the entire NDA/BLA.[149]

However, early analysis of the industry experience with the fast-track program, conducted by the Tufts University CSDD, identified the potential advantages of the regulations.[150] The study surveyed industry participants in the fast-track program and found that many obtained some benefit from formalized interactions with the FDA.[151] When asked which specific programs facilitated the benefits of fast-track designation,

[145] Joseph A. DiMasi and Michael Mannochia, *Initiatives to Speed New Drug Development and Regulatory Review: The Impact of FDA-Sponsor Conferences*, Drug Information Journal, Aug. 15, 1997, at 771; see also Milne and Bergman, supra note 5, at 72 (quoting *Another View on Industry Response to Fast Track Program*, US Regulatory Reporter, Sept. 1998, at 1.

[146] Id. (quoting *Drug Industry Has Not Yet Embraced FDAMA's "Fast Track" Program*, US Regulatory Reporter, Aug. 1998, at 1.

[147] Id.

[148] Id. (quoting *An Interview with Director of the Division of Cardio-Renal Drug Products Raymond Lipicky, M.D.*, US Regulatory Reporter, Oct. 1999, at 3; see also Lisa Piercey, *Life in the Fast Lane*, Signals Magazine, May 23, 2003 (available at http://www.signalsmag.com/signalsmag.nsf/0/ 665186CB53B22AAB88256D4D0053A050). John Jenkins, Director of the Office of New Drugs at the Center for Drug Evaluation and Research (CDER), noted that early cooperation with the FDA is available outside of the fast-track program. "We don't see that (Fast Track) does that much from the perspective of how we interact with a company...If we think you have a product that has real potential to meet a medical need, we are not going to base our decision to interact with you on whether you have Fast Track designation or not."

[149] See Fast-Track Guidance, supra note 113, at 14.

[150] See generally Milne and Bergman, supra note 5, at 71.

[151] Id.

87% of the respondents credited the meetings and correspondence with the FDA, with less than 50% giving credit to the rolling review and accelerated approval mechanisms.[152] When asked what operational factors were responsible for the advantages of the fast-track program, 83% of respondents identified increased interaction with the FDA as an important factor, and 61% specifically lauded the increased face-to-face contact with the agency.[153] Compared to previously existing regulatory mechanisms, the fast-track regulations provided respondents with many more meetings at critical junctures in the clinical development process.[154] Additionally, the study's authors noted there must be some attractiveness to fast-track designation as more fast-track applications were received in the one year since the FDA issued the guidance documents for the FDAMA than there were for Subpart E or H approvals in the ten years prior to the FDAMA. [155]

Notwithstanding the initial positive experiences with the fast-track system, the study left several questions unanswered regarding the overall success or failure of the regulations. Although the fast-track system can impact the entire development and approval life of a drug, the study's authors stated it was too early to determine the effect of fast-track on reducing clinical development time.[156] Additionally, while more than 50% of respondents stated they experienced at least some advantages from fast-track designation, 39% responded that they were still waiting to see if they received any benefits from use of the fast-track programs.[157] Early critics of the fast-track system, who claimed the regulations were primarily for public relations purposes, were left with lingering concerns as 65% of respondents believed the publicity from fast-track designation was at least partly responsible for the benefits from the fast-track regulations.[158]

[152]Id. at 79.
[153]Id.
[154]Id. at 81. Survey respondents had 1.5 times as many meetings at the pre-IND stage, 4 times as many meetings after Phase I, and 6 times as many meetings after Phase II.
[155]Id. at 74.
[156]Id. at 73.
[157]Id. at 79. Of the survey respondents, 9% said fast-track benefited their product to a large extent, 30% said it benefited their product to some extent, 17% said it benefited their product to a minimal extent, 39% said it was too early to tell if their product benefited, and 4% their product did not benefit from fast-track designation.
[158]Id. Respondents rated increased publicity as the second highest operational factor responsible for the benefits of the

The performance record of the fast-track program indicates that the regulations have generally been successful. Nearly fifty drugs and supplemental applications have been approved under the fast-track program.[159] Over the past five years, the FDA has approved new drugs and biologics receiving priority designation in approximately six months, although 2002 had significantly longer review times due to a few exceptional cases.[160] A Tufts University CSDD study from 2003 determined that the average clinical development time for fast-track designated drugs was 2 to 2.5 years shorter compared to non-fast-track designated drugs, and that average total development time, including approval review, was nearly three years shorter.[161] In addition, average approval times for fast-track drugs were one-third the time of standard drug approvals and half the time of priority drug approvals.[162] However, the study found that while fast-track biologics had a shorter approval time compared to standard and priority biologics, clinical development time was 1 to 1.5 years longer.[163] The longer clinical development times for fast-track biologics may be explained by the small sample size and the fact that less biologics compressed clinical development time using accelerated approval mechanisms.[164]

Despite the apparent achievements of the fast-track system, legitimate concerns still remain as to the benefits and the long-term impact of the regulations. One major concern is whether the FDA has been too lenient

fast-track program.

[159]FDA New Drug Approval Report, Fast Track Designated Products Approved Since 1988, updated through Mar. 31, 2005 (hereinafter Fast-Track Approvals). Available at: http://www.fda.gov/cder/rdmt/ internetftap.htm.

[160]See NME/New BLA Approval Times and NDA/BLA Approval Times, supra note 134; see also *FDA Quickens Approval Pace in 2003*, Drug Store News, Feb. 16, 2004, at 35. The FDA attributed the 2002 priority approval times to the effect of a few applications with unusually long regulatory histories.

[161]See Tufts CSDD Fast-Track Study, supra note 5, at 2.

[162]Id.

[163]Id.

[164]Id. The biologics analysis was based on data for six of nine fast-track biologicals, with one product with an exceptionally long development time.

in granting fast-track designations. The FDA has publicly stated that the agency "loosely" interprets the "serious and life-threatening" requirement for fast-track drugs in order to expedite therapies that may not treat immediately life-threatening diseases such as diabetes.[165] According to John Jenkins, director of the Office of New Drugs at the FDA's Center for Drug Evaluation and Research (CDER), the threshold for fast-track qualification is essentially a potential for efficacy in treating an unmet medical need; a potential that often "never materializes."[166] Based on this standard, the FDA has been somewhat generous in granting fast-track designations. In the first quarter of 2005, CDER granted fast-track designation to 53% of applicants, and only denied designation to 20% of applicants.[167] Historically, CDER has been even more liberal, and has granted fast-track designation to nearly 70% of applicants from 1998 to mid-2003.[168] From 1998 to March 2005, the Center for Biologics Evaluation and Research (CBER) has granted fast-track designation to 59% of biologic applicants.[169] Considering that the time it takes for most sponsors to prepare a fast-track request is generally less than the initial FDA estimate of 40 to 80 hours, it comes as no surprise that pharmaceutical companies pursue fast-track designation for as many drug candidates as possible.[170] Many pharmaceutical companies have used the "serious" condition standard to push for a broad range of fast-track designations, thereby "[swinging] wide the regulatory door knocked ajar by the AIDS crisis."[171] Although no analysis has been done as to the frivolity of fast-track applications, a more open definition of "serious" condition is

[165] *Almost Five Years Later: Fast Track Record Slow to Form*, The Food & Drug Letter, Jan. 18, 2002. Sandra Kweder, then acting director of the Office of Review Management at CDER, stated that "fast track helps us achieve our public health mission" by expediting drugs treating conditions with significant morbidity and expanding the definition of an important therapeutic advance to include diseases that aren't necessarily treatments of "serious or life-threatening" conditions.

[166] See Piercey, supra note 148. Jenkins notes that fast-track designation can be based on animal testing in some cases.

[167] FDA New Drug Approval Report, CDER Response to Request for Fast Track Designation FY 2005, updated Mar. 31, 2005 (hereinafter CDER Fast-Track Response). Available at: http://www.fda.gov/cder/rdmt/internetftstats.htm. As of March 31, 2005, 27% of fast-track requests for the fiscal year 2005 are still pending. The median FDA response for 2005 is 51 days; below the FDA fast-track request response goal of 60 days.

[168] See Tufts CSDD Fast-Track Study, supra note 5, at 2.

[169] CBER Fast Track Designation Request Performance Report, updated Apr. 11, 2005 (hereinafter CBER Fast-Track Response). Available at: http://www.fda.gov/cber/inside/fastrk.htm.

[170] See Milne and Bergman, supra note 5, at 76. 41% of respondents stated their fast-track request took 40 to 100 hours to prepare, 35% stated it took 10 to 24 hours to prepare, and 24% stated it took 1 to 5 hours to prepare. The FDA estimated that the preparation of a fast-track request would take 40 to 80 hours; see also Bean, supra note 38, at 887.

[171] David Willman, *How a New Policy Led to Seven Deadly Drugs*, L.A. Times, Dec. 20, 2000, at A1 (quoting Jeffrey A. Nesbit, former Chief of Staff to FDA Commissioner David A. Kessler).

likely to generate an excessive number of fast-track requests that could heavily burden the FDA's limited resources.

A 2003 study by the biotechnology consulting firm, Recombinant Capital, highlights other potential issues with the fast-track system.[172] The study primarily examined therapeutics developed by biotechnology companies, representing nearly half of the products that received fast-track designation between 1998 and 2003.[173] Recombinant Capital found that fast-track designation does not necessarily provide a faster, smoother ride through the FDA approval process and in fact may "flip traditional drug development on its head" by exposing higher product failure rates in later stages of development.[174] Of the 81 products examined in the study, 33 of them had proceeded to Phase III trials.[175] Of the 33 Phase III products, 20 had failed to meet primary endpoints in Phase III or had inadequate Phase III data for FDA approval.[176] Considering the average failure rate for all drugs in Phase III is 30%, the study concluded that fast-track products were twice as likely to fail in Phase III trials.[177] Additionally, the study found that nearly half of the fast-track products that had made it to the NDA stage had either been terminated or were lingering for an average of 23 months.[178]

[172]See Piercey, supra note 148.

[173]Id. Recombinant Capital runs a commercial database or clinical trials with most of the focus on biotechnology firms and their partnerships with larger companies. The Tufts CSDD study appears to have covered a larger number of products from both biotechnology companies and large pharmaceutical businesses.

[174]Id. Traditionally, as a drug moves through the clinical testing phases, the likelihood of proving safety and efficacy increases.

[175]Id.

[176]Id. Although the Recombinant Capital database is limited to potentially higher-risk products, 61% of fast-track products in the study that reached Phase III failed to proceed to NDA/BLA submission.

[177]Id.; see also Joseph A. DiMasi, Ronald W. Hansen and Henry G. Grabowski, *The Price of Innovation: New Estimates of Drug Development Costs*, Journal of Health Economics, Mar. 2003, at 151. The failure rate for drugs in Phase III trials from the late 1990s is about 30%. Failure can be due to lack of efficacy, safety issues, or economic factors.

[178]See Piercey, supra note 148. Of the 81 products in the study, 25 had progressed to the point of NDA/BLA submission. Twelve of those products were approved, but 11 products remained. Five of the 11 remaining products have been terminated, and the other six remaining products lingered.

While somewhat discouraging, these results are not necessarily a condemnation of the fast-track program. First, the fact that a large number of products even proceeded to Phase III suggests that the population of products studied may have been inherently challenged.[179] Second, the data may simply highlight that fast-track products are a high-risk endeavor since they generally address medical conditions where no alternative treatments exist. Third, according to the Tufts CSDD, the fast-track system provides an ancillary benefit by accelerating the inevitable clinical failure of certain experimental drugs.[180] By expediting clinical development to more quickly reach a "fast-fail," the fast-track system can help drug companies redirect resources to other more promising therapies.[181]

The Recombinant Capital study also establishes some legitimacy to the criticisms that the fast-track program is primarily a tool to raise publicity and capital. The FDA has informally stated that larger pharmaceutical companies apply for fast-track designation at a lower rate than smaller startups because the small companies believe it adds value to their business.[182] Recombinant Capital examined public companies with fast-track products and found that stock prices on average jumped 11% and the volume of shares traded increased by 722% on the day fast-track designation was announced.[183] Additionally, 45% of the products studied by Recombinant Capital requested fast-track after the start of Phase III trials, indicating early collaborative benefits may not have been the driving force behind pursuing the designation.[184] As a result, it remains unclear exactly how much of the benefit of fast-track is due to the public relations boost provided by the designation and how much is due to improved regulatory mechanisms.

Outside of the Recombinant Capital study, other concerns still remain regarding the fast-track system.

[179]Id. Christopher-Paul Milne, of the Tufts CSDD, examined the Recombinant Capital results and noted that the products involved in the study may have intrinsically been doomed for failure.
[180]Id.
[181]Id.
[182]Id. (quoting John Jenkins, director of the Office of New Drugs at CDER).
[183]Id. Of the 81 products in the study, only 33 of them were examined for stock price. Data was not available for all companies because some were private and others did not publicly disclose fast-track designation.
[184]Id.

Even though fast-track has been around since 1998, the actual usage and effectiveness of rolling reviews of NDAs/BLAs has yet to be established. According to Jenkins, through 2003, the FDA had conducted rolling review on a "resource available basis."[185] These comments appear to fit with the FDA's initial guidance that approval review may not occur until an entire application has been filed and the potential resource crunch due to a loose interpretation of the "serious" condition requirement.[186] On paper, rolling review seems like an effective mechanism of expediting the approval process, but if the FDA does not have the resources to utilize it, then one of the most tangible benefits of the fast-track system remains in question. The FDA hopes that pilot programs will be able to specifically identify any benefit of continuous marketing applications.[187]

The fast-track program has only been in existence for seven years, and the ultimate success of the program has yet to be determined. Although both the Tufts CSDD and the Recombinant Capital studies examine a limited set of fast-track products, both establish quantifiable benefits and reasonable concerns from the regulations. Nevertheless, the FDA records show that the fast-track system appears to have expedited the development and approval of important medications. Considering the FDA has limited resources to evaluate new disease therapies in the United States, the fast-track program, at the very least, enables reviewers to prioritize drugs that focus on treating important and serious conditions.

Section III. Backlash Against the FDA and Implications for Oncology Drugs

The FDA has made truly great strides in expediting the approval of drugs using the fast-track and accelerated

[185] Id.
[186] See Fast-Track Guidance, supra note 113, at 14.
[187] See Draft Guidance for Industry Continuous Marketing Applications, supra note 126.

approval mechanisms, as analyses of the two regulatory programs show that important life-saving drugs have reached the market faster. Unfortunately, recent criticism of the FDA has some industry observers concerned that the agency may return to a more conservative approach of expediting drug approvals. In particular, the cancer community is extremely worried about the trend set by FDA oncology decisions over the past year. However, after examining the recent track record and policy decisions of the FDA, the concerns of cancer patient advocates may be overstated.

A. General Public Backlash Against the FDA

Recent developments regarding FDA decisions, including the discovery of major safety concerns regarding antidepressant use by children, the withdrawal of two widely used arthritis medications, and the withdrawal of an accelerated approval multiple sclerosis drug, have generated a substantial public backlash against the FDA for failing to fulfill one of its fundamental missions – ensuring the safety of drugs in the United States.[188] These events have created an environment where the FDA is under fire from patients, consumer advocates, the medical community, public policy experts, and members of Congress.[189] Much of the focus of their criticism has been on whether or not the FDA is approving drugs too quickly and without proper post-marketing safeguards. Additionally, some observers feel that the agency has been working harder to protect the pharmaceutical industry rather than the general public.[190] As a result, the fast-track program and accelerated approval have received a great deal of scrutiny over the past year for enabling potentially dangerous drugs to enter the market.

[188]Susan Okie, *What Ails the FDA?*, New England Journal of Medicine, Mar. 17, 2005, at 1063; see also Mathews and Hechinger, supra note 9, at B1.
[189]Id.
[190]See Gorman, supra note 1, at 58.

Historically, fast-track and accelerated approval regulations have been relatively free of controversy. However, in 2000, two withdrawals of drugs approved by priority review elicited criticism that the FDA was loosening guidelines intended to protect the public.[191] The first withdrawal of a high profile, priority reviewed drug came in March of 2000 when the FDA advised Warner-Lambert to pull the diabetes treatment Rezulin from the market.[192] The FDA approved Rezulin in January 1997 after a six-month priority review.[193] Although Rezulin was the agency's fastest approval ever for a diabetes drug, the process was not entirely smooth.[194] The original FDA medical officer assigned to the drug, who actually supported its rejection due to potential liver toxicity, was replaced with a more supportive FDA officer under somewhat questionable circumstances.[195] Rezulin was the first of a new generation of novel compounds to treat adult-onset, type 2 diabetes, and the FDA based its swift approval decision on the drug's unique mode of action and clinical benefit to people who did not respond to other treatments.[196] Over the course of the next three years, Rezulin became a multi-billion dollar success, but several cases emerged of Rezulin users who developed life-threatening liver dysfunction, prompting the drug to be withdrawn from the United Kingdom.[197] In March of 1999, after multiple FDA/Warner-Lambert meetings and label changes, the FDA Endocrine and Metabolic Drugs Advisory Committee reviewed the link between Rezulin and liver toxicity and ultimately decided to restrict the drug to patients who did not respond to other treatments, provided that patients undergo regular liver testing and the label indicated potential liver toxicity.[198] By March of 2000, the FDA

[191]See Food & Drug Letter, supra note 165.
[192]Id.
[193]Robert K. Jenner, *Rezulin: Fast Track to Failure*, Trial, July 2000, at 39.
[194]Id. at 40.
[195]Id.; see also Willman, supra note 171 (7 deadly drugs), at A1; David Willman, *Risk Was Known as FDA OKd Fatal Drug Study*, L.A. Times, Mar. 11, 2001, at A1. The FDA medical officer reviewing Rezulin, Dr. John L. Gueriguian recommended the drug be rejected on the basis of potential liver and heart toxicity, and the drug's ineffectiveness in lower blood sugar. Warner-Lambert allegedly complained about Gueriguian, and he was removed from the review, and his recommendation was extricated from the FDA's files. E-mails have been discovered showing the FDA potentially colluded with Warner-Lambert to have Gueriguian "eased out."
[196]See Food & Drug Letter, supra note 165.
[197]See Jenner, supra note 193, at 40 and 46.
[198]Id. At the advisory committee meeting, a presentation by a medical epidemiologist working for the FDA indicated that physicians were not adequately reading the warning letters, the FDA had probably only received reports of about 10% liver damage cases, and Rezulin appeared to be the main cause of the liver damage and deaths reported. A potentially concerning note

was faced with evidence of hundreds of likely deaths due to Rezulin-linked liver failure and advised Warner-Lambert to withdraw the drug.[199] Part of the withdrawal decision was also based on the fact that two safer drugs with similar modes of action were now available on the market.[200] The public was concerned that the influence of pharmaceutical companies drove the FDA to delay the withdrawal of a drug that was long suspected to be dangerous.[201]

Eight months after the withdrawal of Rezulin, the FDA faced another predicament with a priority-reviewed drug. Glaxo Wellcome's Lotronex was approved in February of 2000 under a six-month priority review for the treatment of inflammatory bowel disease.[202] While the approval process for Lotronex lacked the dubious undertones of Rezulin's review, the FDA immediately began receiving reports of Lotronex users experiencing serious complications requiring hospitalization and/or surgical intervention.[203] Concerned with the newfound risks of Lotronex, the FDA and Glaxo Wellcome released a Medication Guide for consumers and updated the labeling for the drug.[204] By November of 2000, the FDA had received 70 cases of complications with Lotronex, with 34 hospitalizations and three suspected deaths.[205] Glaxo Wellcome voluntarily withdrew the drug from the market, and once again, the FDA faced harsh criticism over the agency's risk/benefit analyses

is that prior to the vote, the FDA appointed two new members to the advisory panel that had financial ties to Warner-Lambert.

[199]See Jenner, supra note 193, at 46; see also David Willman, *Hidden Risks, Lethal Truths*, L.A. Times, June 30, 2002, at A1. By the time Rezulin was taken off the market, over 500,000 patients had taken the drug, 90 patients had experienced liver failure, and 63 patients were confirmed dead due to Rezulin.

[200]See Food & Drug Letter, supra note 165.

[201]See Jenner, supra note 193, at 46; see also David Willman, *Fears Grow over Delay in Removing Rezulin*, L.A. Times, Mar. 10, 2000, at A18.

[202]See Food & Drug Letter, supra note 165.

[203]Id. By June 1, 2000, the FDA received 7 reports of severe constipation, with 6 patients requiring hospitalization and 3 requiring surgery. The FDA also received 8 reports of ischemic colitis, with 4 patients requiring hospitalization. These complications were serious considering irritable bowel syndrome is merely a functional disease that causes discomfort and moderate pain.

[204]Id. The Medication Guide contained FDA approved information for pharmacists to distribute with Lotronex, and the label was updated to clarify the contraindications of Lotronex.

[205]Id.

and the decision to rapidly approve an unsafe drug.[206] In addition to these two priority review drugs, other events, including the Fen-Phen scandal and the passage of the abortion drug RU-486 have marred the FDA's reputation in the past.[207] However, these transgressions pale in comparison to the relatively rapid succession of recent, serious safety controversies and the ensuing public response.

The latest wave of negative events for the FDA began with the discovery of evidence that the agency and manufacturers allegedly withheld adverse event data on the use of selective serotonin reuptake inhibitors (SSRIs) by children.[208] Although the FDA issued a Public Health Advisory in October of 2003 reporting risks of suicidal tendencies in children treated with SSRIs, the issue hit the front pages in the summer of 2004 after New York Attorney General Eliot Spitzer brought a civil suit against GlaxoSmithKline for withholding data on the antidepressant SSRI Paxil.[209] Responding to the data and highly publicized reports of teen suicides, the FDA's advisory committees for Psychopharmacologic and Pediatric Drugs recommended that antidepressants carry a black box warning on the possibility of suicidal behavior in young patients; a recommendation the FDA officially implemented in October of 2004.[210] Needless to say, the FDA and manufacturers came under fire for allegedly not releasing information about adverse events, delaying action by stumbling through the antidepressant investigation, and not supporting conclusive pediatric studies.[211]

[206] Id.

[207] See Bean, supra note 38, at 892. RU-486 was a political problem for many years, which inappropriately impacted its FDA approval. The diet drugs Fen-Phen and Redux represent one of the largest mass tort lawsuits in history, with tens of thousands of users suffering some kind of lung or heart damage. While Fen-Phen was never FDA approved, Redux was approved under alleged campaigns of misinformation and manipulation of FDA officials.

[208] Jill Wechsler, *New Questions On Safety: Vioxx, Vaccines, and SSRIs: Today's Bad News As Tomorrow's Agenda*, Pharmaceutical Executive, Nov. 1, 2004, at 36.

[209] Id.; see also Michael Johnsen, *FDA Mulls Stronger Warning for Antidepressants*, Drug Store News, Oct. 11, 2004, at 8.

[210] Id.; see also Shankar Vedantam, *Depression Drugs to Carry a Warning; FDA Orders Notice of Risks for Youths*, Wash. Post, Oct. 16, 2004, at A1. Clinical trials showed that children taking antidepressants have a 4 percent risk of suicidal thoughts and behavior, compared with a 2 percent risk among children getting placebos. The FDA's black-box warning applies to more than just SSRIs, including antidepressants Wellbutrin, Paxil, Celexa, Lexapro, Prozac, Luvox, Remeron, Serzone, Zoloft, and Effexor.

[211] Id. Other than Prozac, no other antidepressants have been specifically approved to treat depression among children. Doctors who prescribe them are extrapolating from studies that show they are effective in adults. In children with depression,

No sooner than the FDA had finally reached a resolution of the SSRI debacle, the agency was hit with perhaps the biggest drug safety crisis in its history – the withdrawal of Merck's blockbuster arthritis medication Vioxx. Like Rezulin and Lotronex, Vioxx was also approved under a six-month priority review, but unlike the two previously withdrawn drugs, Vioxx was the drug of choice for nearly 20 million Americans.[212] Vioxx was one of a new generation of promising painkillers called COX-2 inhibitors, and the drug seemed to be able to reduce pain and inflammation without the sometimes-fatal gastrointestinal side effects commonly caused by existing painkillers on the market.[213] With the Food and Drug Administration (FDA) granting approval for Vioxx for the treatment of osteoarthritis, acute pain and menstrual pain, Merck began its self-proclaimed "biggest, fastest, and best launch ever."[214] The drug was heavily marketed to physicians and through direct-to-consumer advertising, and by 2004, Merck was earning $2.5 billion in annual Vioxx sales.[215] However, in September of 2004, after years of outside criticism from medical professionals and Merck's own conflicting clinical studies, the company withdrew the drug after receiving definitive proof of what it had feared since the development of Vioxx: that Vioxx significantly increased the risk of heart attack and strokes.[216]

Particularly damaging to the FDA was the substantial public "whistleblowing" by Dr. David Graham, the Associate Director for Science in the FDA's Office of Drug Safety. Graham claimed that the agency

the overwhelming majority of clinical trials have failed to show that widely prescribed drugs are superior to placebos; see also Wechsler, supra note 208, at 36; Okie, supra note 188, at 1063.

[212] *Merck's Earnings Per Share Increase 15% for 1998*, Business Wire, Jan. 26, 1999; see also John Simons and David Stipp, *Will Merck Survive Vioxx?*, Fortune, Nov. 1, 2004, at 90.

[213] Id.

[214] Robert Langreth, *FDA Approval of Vioxx Allows Merck To Compete With New Arthritis Drugs*, Wall Street Journal, May 24, 1999, at B3; see also Merck and Co., Inc., 1999 Annual Report, 1. (Available online at: http://www.merck.com/overview/99ar/99ar_pdf_frameset.html).

[215] Chris Adams, *Merck Ads for Arthritis Drug Attract Regulatory Scrutiny*, Wall Street Journal, Nov. 19, 2002, at B6; see also Simons and Stipp, supra note 212, at 90.

[216] Barbara Martinez, Anna Mathews, Joann Lublin and Ron Winslow, *Expiration Date: Merck Pulls Vioxx From Market After Link to Heart Problems*, Wall Street Journal, Oct. 1, 2004, at A1.

allegedly ignored or attempted to silence earlier reports of Vioxx's adverse effects.[217] In August of 2004, Graham completed an epidemiological study concluding that high doses of Vioxx should never be used due to the cardiovascular risks of the drug.[218] Multiple FDA officials apparently questioned the appropriateness of Graham drawing such a strong conclusion and requested that Graham tone down his message.[219] Ultimately, Graham altered his conclusion to note that the study casted "serious doubt" about Vioxx's safety, and that an estimated 28,000 cardiovascular related deaths could have been avoided by not using Vioxx.[220] Despite this study and a litany of previous epidemiological data, the FDA still did not appear willing to make any changes to its regulation of Vioxx, and even went ahead and approved a supplemental indication to treat juvenile rheumatoid arthritis on September 8, 2004.[221] Two weeks later, Merck received compelling safety evidence from an ongoing clinical trial that indicated Vioxx had cardiovascular risks.[222] On September 30, 2004, Merck withdrew Vioxx from the worldwide market, causing the company's stock price to plunge 27% and its market capitalization to drop $26.8 billion in a single day.[223] In the weeks following, medical experts and an FDA report estimated the casualties caused by the drug could be in the hundreds of thousands.[224]

[217] *FDA, Merck and Vioxx: Putting Patient Safety First?: Hearing Before the Senate Finance Comm.*, 108th Cong. (2004) (statement of Dr. David J. Graham, Associate Director for Science, Office of Drug Safety, Center for Drug Evaluation and Research, Food and Drug Administration).

[218] Anna Mathews, *Did the FDA Minimize Vioxx's Red Flags?*, Wall Street Journal, Nov. 10, 2004, at B1.

[219] Id.; see also Graham, supra note 217; Anna Mathews, *FDA Officials Tried to Tone Down Report on Vioxx*, Wall Street Journal, Oct. 8, 2004, at B2. Allegedly, John Jenkins, Director of the FDA's Office of New Drugs and member of the Office of Drug Safety pressured Graham to change his conclusions because they were inconsistent with the FDA's stance on drug safety. Graham claims that during a meeting, the FDA officials questioned why he had even conducted the study and that one senior manager called the Kaiser study a "scientific rumor."

[220] Id.; see also Anna Mathews, *New Vioxx Study Projects Cases of Heart Attacks*, Wall Street Journal, Oct. 6, 2004, at A2.

[221] See Graham, supra note 217. Even as late as September 22, a week before Merck withdrew Vioxx from the market, Graham claims that directors and senior managers in the FDA's Office of New Drugs and Office of Drug Safety did not believe there was a Vioxx safety issue to deal with that wasn't already covered by the labeling change in 2002; see also *Rheumatoid Arthritis; FDA approves VIOXX for once-daily treatment of JRA*, Med. Letter on CDC and FDA, Oct. 10, 2004, at 86.

[222] Barbara Martinez, Anna Mathews, Joann Lublin and Ron Winslow, *Expiration Date: Merck Pulls Vioxx From Market After Link to Heart Problems*, Wall Street Journal, Oct. 1, 2004, at A1. Unlike previous retrospective, epidemiological studies, the new safety evidence came from a prospective clinical trial; effectively ending Merck's ongoing defense against outside negative epidemiological studies that the clinical trial data showed Vioxx was safe.

[223] Id.

[224] See Simons and Stipp, supra note 212, at 90; see also Eric J. Topol, *Failing the Public Health – Rofecoxib, Merck, and the FDA*, New England Journal of Medicine, Oct. 21, 2004, at 1707 (estimating a potential of 160,000 excess heart attacks or strokes caused by Vioxx).

Public outrage continues to simmer amid questions whether the FDA has become too lenient in approving drugs through fast-track mechanisms. Specifically in response to safety concerns, the agency has advised Pfizer to withdraw a similar COX-2 inhibitor, and added tougher safety warnings to other similar anti-inflammatory drugs.[225] But the public backlash and Graham's provocative claims have spurred multiple evaluations of FDA processes and plans to establish an independent Drug Safety Oversight Board within CDER.[226] Some believe the FDA's decision to rein in the use of several popular painkillers and add further levels of bureaucracy signals a shift in the agency's risk/benefit calculation towards over-caution.[227]

With the FDA being battered from all sides about the agency's inability to regulate drug safety, the withdrawal of the multiple sclerosis (MS) drug Tysabri could not have come at a worse time. Tysabri was the first MS treatment to receive approval in eight years, and based on promising data from a one-year trial, the drug sped to market in November 2004 under Subpart H regulations.[228] Unfortunately, four months later, Tysabri was withdrawn and clinical trials were suspended after the reports of the death of one trial participant from a rare and potentially fatal neurological infection.[229] Because the adverse effect is a very rare condition that is unlikely to be detected in clinical trials, the FDA has yet to receive heavy criticism

[225] Marc Kaufman, *Painkiller Decision Suggests Shift in FDA's Risk-Benefit Equation*, Wash. Post, Apr. 11, 2005, at A3. Although Merck initiated its Vioxx withdrawal, Pfizer withdrew its similar drug Bextra only reluctantly and voiced concern that the FDA was changing how it judges the value of medications. Evidence showed Bextra also could increase the risk of heart attacks, strokes and a potentially fatal skin disease.

[226] See Graham, supra note 217; see also *FDA, Merck and Vioxx: Putting Patient Safety First?: Hearing Before the Senate Finance Comm.*, 108th Cong. (2004) (statement of Dr. Sandra L. Kweder, Deputy Director, Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration); *FDA's Safety Oversight Board Proposal Met With Mixed Reviews*, Washington Drug Letter, Feb. 21, 2005.

[227] See Kaufman, supra note 225, at A3. Sam Kazman, chief counsel of the Competitive Enterprise Institute, states "the traditional FDA response to criticism is to revert to deadly overcaution...When the agency is criticized about a drug, its natural reaction is to withdraw it and become more cautious about approving others in the future." The Pharmaceutical Research and Manufacturers of America also recognized "a perceived shift in the risk-benefit evaluation."

[228] *Inside The Industry Tysabri: Sales Suspended After MS Drug Linked to Infection*, American Health Line, Mar. 1, 2005. Typically, MS drugs require a two-year trial, but Tysabri was found to reduce the MS relapse rate by 66% compared with a placebo, and by 54% in combination with another MS treatment Avonex.

[229] Id.; see also Mathews and Hechinger, supra note 9, at B1. Biogen Idec and Elan Corp., the manufacturers of Tysabri stated another patient may be afflicted with PML. Both patients were enrolled in clinical trials examining the combination of Tysabri with another MS treatment.

for accelerating the approval of Tysabri.[230] Nevertheless, the drug's suspension has brought accelerated approval procedures under the public's microscope, and is bolstering concerns that the FDA is approving drugs with limited evidence of safety and efficacy.[231]

The trio of negative events has placed the FDA in an unprecedented situation where the pendulum could easily swing back towards a tougher, more risk-averse approval policy. Public furor has reached new highs behind statements like that of Dr. Graham that "the FDA, as currently configured, is incapable of protecting America against another Vioxx" and that "we are virtually defenseless."[232] The question is whether or not a return to a more cumbersome, paternalistic FDA is the best solution for the United States.

B. The Cancer Community's Fear of a More Risk-Averse FDA and ODAC

One of the unsettling implications of the potential over-reaction to the FDA's drug safety effort is the effect the backlash will have on approvals of important, life-saving cancer treatments. Since the fight to gain access to Laetrile in the 1970s, the cancer community has been one of the strongest and passionate forces behind reforms of FDA approval policies.[233] Prior to the implementation of accelerated approval and fast-track mechanisms, cancer patient advocates long believed that the FDA's drug approval policy was far too conservative and paternalistic given that cancer is such a deadly disease.[234] As a result, any impetus

[230]Id.; see also Bernadette Tansey, *Hard Sell: How Marketing Drives the Pharmaceutical Industry*, San Francisco Chronicle, Mar. 3, 2005, at C1.
[231]See Mathews and Hechinger, supra note 9, at B1.
[232]See Graham, supra note 217.
[233]See Hutt & Merrill, supra note 46, at 557; see also Rovner, supra note 62 (Lancet FDA Speeds Up...), at 1038.
[234]Id.

towards a return to more restrictive approval standards is understandably a serious concern for the cancer community.

Compared to the average member of the public, cancer patients have an entirely different perspective of the FDA's risk-benefit calculus for drug approvals. Because many oncology drugs cannot discriminate between cancerous cells and non-cancerous cells, cancer patients are often presented with the painful tradeoff between burden of treatment and burden of disease.[235] Unlike reviews for other medicines, the FDA approaches cancer drug approval with a viewpoint that efficacy is of greater concern than toxicity because significant toxicity is generally considered acceptable for oncology drugs given the severe and often fatal nature of the disease being treated.[236] Because the impact of cancer is far more damaging than the treatments used to stop the disease, cancer patients have a far higher risk-tolerance than the rest of the population.

The fact that realistically, many more cancer patients are dying from the disease than from adverse drug events places the FDA in a precarious position of balancing consumer protection with a heightened importance of personal autonomy.[237] Cancer patients have a vested interest in determining both how they want to live and how they want to avoid death, and to maximize personal autonomy, they desire less intervention by the FDA.[238] Since cancer patients know that nearly every oncology treatment carries a significant level of risk, they believe that in the face of death, the FDA should not be restricting the approval of innovative drugs based on a risk-tolerance calculation influenced by the general public.[239] Although recognizing

[235] *The FDA's Drug Approval Process: Up To the Challenge?*: Hearing Before the Senate Health, Education, Labor and Pensions Comm., 109th Cong. (2005) (statement of Nancy Davenport-Ennis CEO, National Patient Advocate Foundation).
[236] Id.
[237] Id.; see also *FDA Oncologic Drugs Advisory Committee Meeting*, Mar. 12, 2003, at 13 (statement of Steve Walker, FDA Advisor to the Abigail Alliance for Better Access to Developmental Drugs). According to Walker, "we lose about 800,000 or 900,000 every year to cancer and they have nowhere to go except clinical trials which are too small and too restrictive."
[238] Id.
[239] See Davenport-Ennis, supra note 235.

personal autonomy involves a requisite level of information, cancer patients are willing to make decisions without all the information due to their desperate situation.[240] As Michael Greenberg argues, conservative approval policies can overlook the preferences and needs of persons whose values significantly depart from those of the general public.[241] Expediting drugs onto market spreads the risk from some of the most helpless, endangered citizens to a larger population. Therefore, any public momentum that threatens to shift the risk back to those with life-threatening diseases is a worrisome development for cancer patients who have fought so hard over the past two decades to accelerate drug approvals.

Contrary to recent public sentiment, the cancer community not only fears the prospect of more burdensome regulatory and bureaucratic requirements, but also believes that current mechanisms to expedite drug approvals are inefficient. Outside of the fact that a more conservative FDA approach would unravel the gains made by the cancer community in the past twenty years, cancer advocates feel that fast-track and accelerated approval should have hastened the approval of more oncology drugs.[242] Among their concerns is that the agency lacks a sense of urgency in supporting the spirit of accelerated approval regulations, and instead has overemphasized adverse effects, statistics and process.[243] Additionally, they believe that limited regulatory acceptance of surrogate endpoints and an overly restrictive definition of clinical benefit have negatively impacted the FDA's risk/benefit calculus for many desperate cancer patients.[244] For instance, the Abigail Alliance for Better Access to Development Drugs, a major political supporter of expediting approvals, believes that while the current regulations are "good approval mechanisms," the standards for approving drugs

[240]Michael Greenberg, Information, Paternalism, and Rational Decision-Making: The Balance of FDA New Drug Approval, 13 Alb. L.J. Sci. & Tech. 663, 671-74 (2003).
[241]Id. at 676.
[242]See Walker, supra note 237, at 11.
[243]Id. at 11-12.
[244]Id.

based on surrogate endpoints needs to be at the very least kept the same or lowered.[245] Considering the recent, substantial scrutiny of the FDA's drug safety efforts, the cancer community's viewpoint on approval standards is nearly the opposite of the rest of the general public. This dichotomy embodies the dilemma the FDA faces in weighing broad social welfare against the needs of society's most vulnerable.

Taking into account the FDA's oncology track record in recent years, it is no surprise that patient advocates and the media perceive that the public backlash against the agency heightens the risk of tightening the standards for expediting oncology drug approvals. The cancer community originally had cause for concern based on the discussions at a March 2003 ODAC meeting examining the challenges of accelerated approval.[246] At that meeting, the FDA presented the status of post-marketing validation trials for eight products receiving Subpart H approval between 1995 and 2000.[247] The ODAC heard the startling evidence that the average time between granting of accelerated approval and the completion of confirmatory post-marketing studies was projected to be ten years.[248] The FDA highlighted the fact that not only were there problems convincing patients to enroll in clinical studies after a drug had hit the market, but there seemed to be a loss of sense of urgency by drug manufacturers in completing the studies.[249] The loss of the manufacturer's sense of urgency was illustrated by the confirmatory studies for Ontak.[250] In the years following accelerated approval, Ontak's manufacturer was only able to enroll on average eight patients a year into confirmatory studies; a rate of enrollment far below the acceptable standard for pre-marketing clinical trials.[251] The ODAC was

[245] Id. at 13-15.
[246] *FDA Oncologic Drugs Advisory Committee Meeting*, Mar. 12-13, 2003.
[247] *FDA Oncologic Drugs Advisory Committee Meeting*, Mar. 12-13, 2003 (statements by Dr. Ramzi Dagher, FDA Division of Oncology Drug Products).
[248] Id.; see also Thomas R. Fleming, *Surrogate Endpoints and FDA's Accelerated Approval Process*, Health Affairs, Jan./Feb. 2005, at 75.
[249] Id.; see also *FDA Oncologic Drugs Advisory Committee Meeting*, Mar. 12, 2003, at 249 (statements by Thomas R. Fleming, ODAC consultant, Professor and Chair of Biostatistics, Univ. of Wash.).
[250] Id.; see also Fleming, supra note 248, at 76.
[251] Id.

also surprised to learn that the FDA did not have clear plans for dealing with an accelerated approval drug where validation trials were not conclusively positive.[252] For instance, the initial confirmatory studies for Ethyol injection indicated a minimal treatment benefit, but the treatment continued to be marketed as an accelerated approval drug.[253] Comments regarding the "sobering" evidence presented by the FDA were certainly not encouraging for the cancer community. Dr. Bruce Cheson, a member of the committee stated, "[t]here will be...a little more vigilance in the decision making by the members of the committee...and maybe a little more reluctance to approve certain drugs on some of the meager evidence which they're being presented."[254]

Despite the pessimistic tone set by the ODAC meeting, cancer patient advocates seemed appeased by the tenor of the FDA under the helm of Mark McClellan. McClellan was President George W. Bush's first appointee as FDA commissioner in November 2002.[255] Under the stewardship of McClellan, members of the pharmaceutical industry, financial analysts, and patient advocates perceived a marked change in attitude towards expediting drug approvals.[256] In June of 2003, McClellan announced his initiative to improve the use of fast-track and accelerated approval mechanisms for non-immediately life-threatening diseases such as diabetes and obesity.[257] That same year also brought the accelerated approval of three new oncology drugs, Iressa, Velcade, and Bexxar.[258] The approval of Iressa is particularly noteworthy because it was approved with very low clinical trial response rates of 10-20 percent, thereby fueling speculation that the

[252]Id.; see also *FDA Oncologic Drugs Advisory Committee Meeting*, Mar. 12, 2003, at 19.
[253]Id.; see also Fleming, supra note 248, at 76.
[254]*FDA Oncologic Drugs Advisory Committee Meeting*, Mar. 13, 2003 at 165 (statements by Dr. Bruce Cheson, ODAC member).
[255]See Okie, supra note 188, at 1063.
[256]Thomas J. Bliley Jr., *FDA at a Crossroads*, Wash. Times, May 3, 2004, at A15; see also Gloria Lau, *Cancer Experts Say FDA Never Softened Stance on Medicines*, Investor's Business Daily, May 24, 2004, at A13.
[257]Christopher Rowland, *FDA Chief Looks to Speed Diabetes, Obesity Drugs*, Boston Globe, Jun. 4, 2003, at A1.
[258]See Roberts and Chabner, supra note 6, at 503.

FDA and ODAC was relaxing the standards for cancer drugs.[259] Around the same time as the Iressa approval, McClellan seemed to echo President Clinton's comments that the FDA and pharmaceutical companies should be "partners, not adversaries", by declaring that the FDA was more "industry friendly."[260]

While the cancer community seemed encouraged by McClellan's tenure as commissioner, their contentment was cut short in March of 2004 when McClellan became administrator of the Centers for Medicare and Medicaid Services.[261] Since that time, cancer patient advocates, the pharmaceutical industry, the media, and financial analysts have allegedly witnessed the pendulum swinging backwards with a growing trend of caution infiltrating the FDA and ODAC. The first signal that the FDA may be becoming more restrictive in approving cancer drugs came in May of 2004 when the ODAC examined the applications for two fast-track cancer medications, Genasense and RSR13.[262] The two drugs were up for approval with the agency at a crossroads; many observers were interested in how flexible the ODAC would be considering the two drugs had limited statistical efficacy evidence.[263] Ultimately, the ODAC and the FDA rejected the accelerated approval of both drugs.[264] The ODAC found that clinical trial data for Genasense showed no statistically significant evidence of increased survival rates for melanoma patients, and RSR13's clinical trials were poorly structured and also lacked statistically significant evidence of effectiveness in treating breast cancer patients.[265]

Despite the fact that the FDA did approve multiple other cancer treatments following the Genasense/RSR13 meeting, cancer patient advocates viewed the ODAC's recommendation to reject the accelerated approval

[259] See Lau, supra note 256, at A13.
[260] Id.; see also Willman, supra note 171, at A1.
[261] See Okie, supra note 188, at 1063.
[262] *FDA Oncologic Drugs Advisory Committee Meeting*, May 3-4, 2004.
[263] See Bliley Jr., supra note 256, at A15; see also Lau, supra note 256, at A13.
[264] Id.
[265] See *FDA Oncologic Drugs Advisory Committee Meeting*, May 3-4, 2004; see also *Regulatory News FDA: Decisions on Cancer RX Could Indicate New Agency Trend*, American Health Line, Apr. 26, 2004, at 7.

of Marqibo in December of 2004 as a dangerous precedent.[266] Inex Pharmaceutical applied for accelerated approval of Marqibo as a treatment for relapsed, aggressive non-Hodgkin's lymphoma.[267] The company was hopeful because Marqibo was getting a 25% response rate and there were no approved drugs to treat the condition on the market.[268] Unfortunately, the ODAC and the FDA criticized the design and analysis of the clinical data and recommended against approval of the drug.[269]

While the ODAC has rejected accelerated approvals in the past, the committee not only rejected the drug based on statistical evidence, but also because other available oncology drugs treated the same condition through off-label regimens.[270] Fast-track and accelerated approvals are generally for treatments for an unmet need, and as a result, candidate drugs are typically compared to "available therapies."[271] While the FDA had narrowly defined "available therapy" in the past in order to reduce the hurdles for drugs to reach the market through accelerated pathways, the ODAC construed "available therapies" in oncology as including unapproved off-label uses of drugs with "compelling" evidence of efficacy in the scientific literature.[272] ODAC's new practice of comparing new drugs to unapproved uses of available drugs signaled a shift in policy that could make it harder for cancer drugs to get approved in the future.[273] Additionally, members of ODAC, the FDA, and outside advisers all expressed concern that pharmaceutical companies may be abusing the accelerated approval mechanisms.[274] Several members of the ODAC praised the committee's chair, Dr. Silvana Martino, for "speaking the truth" that pharmaceutical companies have continuously pressured the

[266] See Accelerated Approvals – Biologics, supra note 131; see also *FDA Oncologic Drugs Advisory Committee Meeting*, Dec. 1, 2004; Gottlieb, supra note 10.
[267] Martin Braun, *Inex Gets Sucker-Punched by U.S. Drug Regulators*, The Globe and Mail, Dec. 4, 2004, at B2.
[268] Id.
[269] Id. The FDA questioned the validity of some of the clinical data and disregarded it, dropping the response rate to 12%.
[270] Id.
[271] See *FDA Oncologic Drugs Advisory Committee Meeting*, Dec. 1, 2004, at 293-95 (statements of Dr. Maitreyee Hazarika).
[272] *Briefing and Opinion: New Drug Approval*, The Journal Editorial Report, Dec. 10, 2004 (quoting Scott Gottlieb, a former senior policy adviser to the Commissioner of the FDA). Available at: http://www.pbs.org/wnet/journaleditorialreport/121004/briefing.html.
[273] See Gottlieb, supra note 10.
[274] See *FDA Oncologic Drugs Advisory Committee Meeting*, Dec. 1, 2004, at 386-69 (statements of Dr. Silvana Martino, Acting Chair of ODAC; Richard Pazdur, FDA Division of Oncology Drug Products; Dr. Otis W. Brawley, ODAC member).

FDA to approve drugs with lower response rates and participants.[275] Martino noted:

> I have sat on this committee for about three years now, and it almost occurs to me that we are looking for what is the least amount of data to be convincing, and I think that is the wrong approach, but that is what I see that we do, especially with accelerated approval, is what is the least amount that you can show me, to which I will then give you a reward for that. I actually think that as a medical community, we have to rethink what our objectives are and what our purpose are.[276]

The ODAC's new perspective on accelerated approval has generated fear in cancer patient advocates that the FDA may now require overwhelming statistical efficacy evidence.[277] The ODAC's more cautious approach has been interpreted by some as a response to the general backlash against the FDA.

Three months after the ODAC's decision to reject Marqibo, the cancer community was dealt another blow when confirmatory studies for Iressa, the accelerated approval drug heralded as a signal the FDA was becoming more lenient on cancer treatments, failed to show the drug prolonged lives.[278] Iressa represents the first time the FDA is faced with an accelerated approval cancer drug with unfavorable post-marketing studies, and the FDA's response will likely set a precedent for how the agency deals with failed validation trials in the future.[279] The ultimate fate of Iressa is yet to be determined, as the FDA will not make a regulatory decision on the drug until June 2005.[280] However, the public response has already turned negative with the consumer advocacy group Public Citizen petitioning the FDA to withdraw the drug, citing multiple failed

[275] Id. at 373.
[277] See Gottlieb, supra note 10; see also Braun, supra note 267, at B2.
[278] Renee Twombly, *FDA Oncology Committee Debates Iressa's Status Following Negative Trial Results*, Journal of the National Cancer Institute, Apr. 6, 2005, at 473.
[279] *Iressa Decision to Set Precedent for Negative Fast-Track Trials*, FDA Week, Mar. 11, 2005.
[280] *FDA Oncologic Drugs Advisory Committee Meeting*, Mar. 4, 2005, at 12-13 (statements of Dr. Richard Pazdur, FDA Division of Oncology Drug Products). The FDA has withdrawn the drug from the market because certain patients with a specific genetic profile responded well to Iressa, and further statistical analysis needs to be completed on the confirmatory trial data. However, a "Dear Doctor" letter was sent out advising physicians to consider other treatments.

clinical trials and evidence of Iressa-related deaths in Japan.[281] Even more damning is the open remorse exhibited by at least one ODAC member who claims the committee and Iressa's manufacturer, AstraZeneca, mishandled the drug and that patients are owed an apology.[282] The fact that an accelerated approval drug failed confirmatory trials, coupled with the statements by ODAC and Public Citizen's petition, further worries the cancer community that the accelerated approval of oncology treatments is threatened in the future.[283] As the events of the past few months compound on one another, the specific actions within the oncology arena coupled with the general public backlash against the FDA have created a perception that the embattled FDA may adopt a more conservative framework for evaluating cancer drugs.

C. A More Risk-Averse ODAC and FDA: Media Myth?

While the events over the past year appear to cast a grim outlook on the expedited approval of cancer drugs, the cancer community's fears of an overly cautious ODAC and FDA may be unreasonable and based on hyperbole perpetrated by the media. First of all, claims that the FDA is more restrictive in the post-McClellan era fail to recognize that McClellan did not have any direct influence over ODAC decisions.[284] Although McClellan may have presented sound bites that indicated the FDA was open to more collaboration with pharmaceutical companies, he never stated the agency would begin approving drugs by lowering safety and

[281] Sidney Wolfe, Peter Lurie, and Elizabeth Barbehenn, Petition to the FDA to Remove the Cancer Drug Gefitinib (IRESSA) From the Market, HRG Publication #1728, Mar. 4, 2005. Available at: http://www.citizen.org/publications/release.cfm?ID=7369&secID=1655&catID=126.

[282] *FDA Oncologic Drugs Advisory Committee Meeting*, Mar. 4, 2005, at 124-25 (statements of Dr. Otis Brawley, ODAC Member). Brawley noted, "The fact remains that this drug has been available for 7 years, and we still haven't figured out exactly how this drug should be used in the treatment of lung cancer...if we had held off in getting it available to people two, three years ago, those studies would have been done...the failure to totally find and totally categorize that estrogen receptor is the reason why we are in the pickle that we are in today."

[283] *FDA Oncologic Drugs Advisory Committee Meeting*, Mar. 4, 2005, at 97-100, 132-33 (statements of Laurie Fenton, President of the Lung Cancer Alliance; Sheila Ross, patient representative for Iressa); see also Andrew Pollack, *FDA Panel Weighs Fate of a Drug for Cancer*, NY Times, Mar. 5, 2005, at A8.

[284] See Lau, supra note 256, at A13 (quoting Paul Goldberg, editor of The Cancer Letter, who stated, "I bet half of [ODAC] wouldn't recognize McClellan if he walked into a room without a name tag...Their recommendations are guided by data."

efficacy standards.[285] Talk of a post-McClellan FDA conservatism was likely a construct of the pharmaceutical industry and the financial markets to cover up for over-confident speculation regarding oncology drug approvals following the approval of Iressa with such a low response rate.[286]

Regarding the effect of the recent public backlash against the FDA, many doomsayers are quick to forget that most of the concerns regarding accelerated approval that the ODAC has "suddenly" developed actually existed back in March of 2003. Despite ODAC's critical examination of Subpart H, the committee continued to recommend several oncology drugs for accelerated approval and the FDA granted fast-track status to multiple experimental candidates.[287] In fact, not only did the FDA grant accelerated approval to Iressa, Velcade, Bexxar, and two Gleevec supplemental applications in the months after the ODAC aired its concerns about Subpart H, but the agency also approved Erbitux, Alimta, Clolar, and supplemental applications for Femara and Bexxar in 2004.[288] Clolar, which was even approved without confirmed validation trial plans, was recommended for approval at the same ODAC meeting where Marqibo was rejected.[289] Moreover, the ODAC has repeatedly stated its support for the fast-track and accelerated approval regulations, which is demonstrated by the fact there are more than fifty oncology drugs in development with fast-track designation.[290] Even though members of ODAC have made statements indicating a desire to "rethink objectives" and perhaps require more rigorous clinical trial data for accelerated approval, the committee's actions speak louder than words. In the wake of the Iressa confirmatory trials outcomes, the ODAC's comments appear to be a vague warning to pharmaceutical companies to not come in aiming for the lowest possible response

[285]Id. (quoting Dr. Michael Friedman, former FDA deputy and commissioner).
[286]Id.
[287]See Appendix A, Fast-Track and Accelerated Approval Oncology Drugs.
[288]See Accelerated Approvals – NDAs and Accelerated Approvals – Biologics, supra note 131. The FDA granted accelerated approval to a new indication of Femara for the treatment of breast cancer in women who have completed tamoxifen therapy.
[289]See *FDA Oncologic Drugs Advisory Committee Meeting*, Dec. 1, 2004, at 16.
[290]See *FDA Oncologic Drugs Advisory Committee Meeting*, Mar. 13, 2003 at 200 (statements of Dr. Richard Pazdur, FDA Division of Oncology Drug Products); see also *FDA Oncologic Drugs Advisory Committee Meeting*, Dec. 1, 2004, at 370-71; Appendix A.

rates, but the committee has not set unreasonable expectations for clinical trial effectiveness. Clearly, the ODAC does not have a blanket rule of over-caution in effect, and the fact that two new oncology drugs and two new oncology indications were granted accelerated approval after McClellan left for his new post indicates the purported policy shift in the post-McClellan era is a misperception created by the media and biased observers.[291]

The decisions faced by ODAC in the current environment are no different than the balancing of risks and benefits the committee has undertaken in years past. True, there is a growing general public sentiment for caution, but because the cancer community's risk-tolerance is significantly different than that of other consumers, the ODAC must still weigh the heightened importance of personal autonomy versus a paternalistic need to protect cancer patients from dangerous or ineffective drugs. Although critics of the ODAC's recent actions claim there is a disturbing trend towards restricting approvals, they easily overlook the fact that the Subpart H oncology drugs rejected by the committee had serious clinical data deficiencies. While the ODAC saw some positive effects from Genasense, the clinical trial data showed no significant evidence of increased survival rate and the committee believed both the medical community and the drug's sponsor did not have enough of an understanding of the drug to optimize its utility.[292] RSR13 showed limited evidence that the drug could extend the lives of breast cancer patients by 4.1 months, but the evidence was fished out of the data from a larger study and did not meet the statistical hurdles for effectiveness.[293] Marqibo also had questionable response rate data, but even at the drug's highest reported response rate, other well

[291] See Okie, supra note 188, at 1063. McClellan left to become administrator of the Centers for Medicare and Medicaid Services in March 2004. Alimta was granted accelerated approval in August of 2004, and Clolar was granted accelerated approval in December of 2004. The Femara supplemental NDA was granted in November of 2004. The Bexxar supplemental BLA was granted in December of 2004.

[292] See *FDA Oncologic Drugs Advisory Committee Meeting*, May 3, 2004.

[293] Id.; see also Lau, supra note 256, at A13.

established off-label regimens had better response rates.[294] However, for each of these drugs, there were patients who had positive responses. Does this mean the FDA should be granting accelerated approval for these drugs? The reality is that once these drugs are not approved, their sponsor companies may terminate their development due to financial constraints.[295] At the same time, were the FDA to approve them, not only would there be drugs available on the market that are ineffective for many patients, but enrollment in clinical trials to confirm the effect of the drugs would be severely limited.[296]

The purpose of accelerated approval is to rapidly introduce drugs intended to treat life-threatening diseases when the inadequacy of existing treatments creates an immediate unmet medical need. In the case of Marqibo, the drug does not fulfill the immediate need for a non-Hodgkins lymphoma treatment because it has a lower response rate than other existing therapies.[297] While those alternative therapies are not "approved" under the FDA rubric, they do represent the current standard of care for treating relapsed, aggressive non-Hodgkins lymphoma.[298] Although cancer activists claim that there are some patients responding to Marqibo and that all non-Hodgkins lymphoma sufferers should be given the chance to decide among therapies, the rejection of accelerated approval does not mean that Marqibo cannot ever enter the market; it means that Marqibo cannot enter the market early based on limited clinical data when other more effective therapies exist.

To the lay observer, the ODAC and FDA's decision to reject these marginal cancer drugs goes directly against recognizing the personal autonomy of cancer patients to choose which therapy they want to use to

[294]See *FDA Oncologic Drugs Advisory Committee Meeting*, Dec. 1, 2004.
[295]Id.
[296]Id.
[297]Id.
[298]Id.

survive. The regulation of drugs by the FDA has been viewed as a justified form of paternalism because it forces manufacturers to develop a wealth of data supporting a drug's safety and effectiveness, while also protecting consumers from unquantified risks.[299] In theory, personal autonomy may be maximized if there were no regulation of drugs and patients could weigh the pros and cons of a full variety of different treatments. However, most members of society, since the time of the Elixir of Sulfanilamide, have welcomed the FDA's constraints on individual freedom because drug regulations generate a great deal of information and also protect the public health. Even though cancer patients in particular have a lower risk threshold and are willing to make decisions with imperfect information, a completely unregulated market would likely make it impossible for these desperate patients and their caregivers to identify the safest and most effective treatments. Increasing the number of drugs to choose from without the requisite insights to guide decisions, and allowing access to costly, potentially toxic, and questionably effective treatments does not seem to be in the best interests of patients. Therefore, some form of FDA paternalism is necessary in order to check unsafe, irrational behavior influenced by the devastating consequences of terminal illnesses.

Based on this policy standpoint of the FDA as a valuable gatekeeper, the ODAC's recent decisions reflect a careful balancing of enabling personal autonomy while simultaneously protecting vulnerable cancer patients. The rejections of Genasense, RSR13, and Marqibo on the basis of poor clinical trial data send signals to future applicants that they must design better studies to provide more useful information. While the cancer community may think that these rejections stifle individual freedom by reducing the number of choices, the decisions in fact improve personal autonomy by forcing the creation of better information on which patients can base their potentially life-saving decisions. Additionally, because some experimental therapies are still available to patients through the FDA's expanded access programs, there is still the opportunity for patients

[299] See Greenberg, supra note 240, at 672.

who have a positive response to make enhanced personal autonomy decisions based on the availability of Subpart H rejected drugs. From a public health perspective, the ODAC's decisions may seem paternalistic, but they do serve to mitigate cancer patients' exposure to risk. In the case of Marqibo, alternative therapies with proven effectiveness already exist on the market, and the introduction of an inferior product could confuse and ultimately harm cancer patients. If the FDA approved Genasense and RSR13, the agency could endanger the lives of cancer patients who choose to use drugs with very limited effectiveness. Although maintaining rigorous clinical trial standards could marginally increase the number of cancer deaths due to lack of access to a treatment, if patients and doctors don't have the proper amount of information or are using products with limited effectiveness, then there could be a far greater number of unnecessary fatalities. Considering the fact that the ODAC and the FDA have continued to expedite oncology drugs in the wake of the public backlash, the agency's actual risk/benefit calculus does not seem to have changed significantly from prior years. Even if the pendulum swings back a little, the shift could be considered positive for cancer patients because it lowers their exposure to risky medicines and enables them to better exercise their personal autonomy by making more informed decisions.

Section IV. FDA & ODAC Opportunities to Reform

Despite the fact that the ODAC does not appear to have returned to a more conservative approach toward oncology drug approvals, there are forces at work that could drive the FDA to implement more restrictive mechanisms for all drug approvals as a whole. The FDA has already announced plans to establish a Drug Safety Oversight Board to oversee the management of drug safety issues and provide emerging information

to doctors and patients about the risks and benefits of pharmaceutical products.[300] Additionally, Senate Finance Committee Chairman Chuck Grassley and Senator Christopher Dodd are expected to introduce a bill establishing a truly independent center for drug safety that would report directly to the FDA commissioner.[301] The safety center would not have sole authority to withdraw a drug from the market or hold veto power of new drug approvals, but it would clearly create another level of bureaucracy to an already complicated approval process.[302] Particularly troublesome is the thought that a new agency would decentralize the medical expertise for a given drug because there would have to be separate experts involved in reviewing the drug for approval and for evaluating post-approval safety.[303] While the likelihood of the passage of the Grassley-Dodd bill is unknown, this wave of public outrage and calls for congressional activity provide the FDA and ODAC with an excellent environment to push for improvements to the fast-track and accelerated approval mechanisms for cancer drugs that appease both patient advocates and drug safety critics.

First, the FDA can establish a clear process to use when validation trials for an accelerated approval product fail to show conclusively positive results. To date, no accelerated approval cancer drug has ever been withdrawn, and for over twelve years, the agency has held a vague threat over manufacturer's heads that a product failing confirmatory trials *may* be withdrawn from the market.[304] Iressa's failed validation trials place the FDA and ODAC at a unique milestone, with the chance to determine exactly what the agency will do when an accelerated approval drug's confirmatory trials show a lack of effectiveness.[305] As it stands now,

[300]See Kweder, supra note 226.
[301]*Grassley-Dodd Drug-Safety Bill Coming; Enzi Mulls Need for Legislation*, Wash. Drug Letter, Apr. 11, 2005.
[302]Id.
[303]Anna Mathews and Heather Won Tesoriero, *FDA Official Assails Agency on Monitoring of Risks*, Wall Street Journal, Nov. 19, 2004, at A1. Currently, the medical experts in the OND are considered to be the most familiar with how a specific drug works. Creating an independent safety office would require the hiring of another physician or scientist who would have to become an expert in a specific drug, but sit outside of CDER, thereby reducing efficiencies.
[304]See *FDA Oncologic Drugs Advisory Committee Meeting*, Mar. 12, 2003, at 17 (statements of Dr. Robert Temple, Director of FDA Office of Medical Policy).
[305]It should be noted that Tysabri, the accelerated approval multiple sclerosis drug, was voluntarily withdrawn from the market by its manufacturer.

the accelerated approval regulations allow a drug with potential clinical benefit, but also potential serious safety risks that cannot be detected from relatively short-term trials, to be marketed almost indefinitely.[306] Because accelerated approval involves exposing cancer patients to a calculated, but higher risk, confirmatory trials to prove safety and efficacy must be conducted.[307] If those trials fail, the FDA should respond strongly by either withdrawing the drug or severely restricting it. In the case of Iressa, perhaps the FDA can leave the drug on the market but restrict its use to those patients who have already responded positively to the treatment. Leaving the drug on the market with a strong restriction should appease both cancer activists who claim that patients are stockpiling Iressa, and safety advocates who think the drug is dangerous. By setting a precedent with Iressa, the FDA can enhance predictability of the agency's post-approval decision-making, send a signal to companies pursuing accelerated approval that confirmatory studies must produce good information, and at the same time, encourage pharmaceutical companies to only apply for accelerated approval with drugs that are truly likely to be successful in post-marketing studies.

Another significant area for the FDA to take action on is ensuring manufacturers complete confirmatory trials in a timely fashion. Although the accelerated approval regulations do not require validation studies to be ongoing at the time of approval, drug manufacturers must validate pre-market safety and effectiveness data with post-market clinical trials in order to move from a conditional approval to a full approval status.[308] As the accelerated approval of Clolar in December of 2004 shows, even though the FDA expects validation trials to be underway at the time of approval, the agency is willing to grant Subpart H approval without identification of confirmatory studies.[309] Unfortunately, the FDA has not been successful in prompting

[306]See Fleming, supra note 248, at 76; see also Table 1.
[307]See Shulman and Brown, supra note 5, at 514-15.
[308]Id.
[309]See *FDA Oncologic Drugs Advisory Committee Meeting*, Dec. 1, 2004, at 16.

pharmaceutical manufacturers to finish follow-up studies on accelerated approval drugs. As seen in Table 1, only ten out of twenty-nine accelerated approval oncology drugs, biologics, or supplemental applications have converted to full approvals.

As the ODAC examined in the March 2003 meeting, the average time between the granting of accelerated approval for an oncology drug and the completion of confirmatory studies is ten years.[310] Based on these lengthy delays between Subpart H approval and the conclusion of validation studies, accelerated approval almost becomes

[310]See Fleming, supra note 248, at 75.

Drug/Biologic (Trade Name)	Approval Year	Indication	Post-Marketing Status
Liposomal doxorubicin (Doxil)	1995	Kaposi's sarcoma	Not yet upgraded
Dexrazoxane (Zinecard)	1995	Reduction of doxorubicin toxicity	Full approval
Amifostine (Ethyol)	1996	Reduction of cisplatin toxicity	Not yet upgraded
Docetaxel (Taxotere)	1996	Breast cancer	Full approval
Irinotecan (Camptosar)	1996	Colon cancer	Full approval
Capecitabine (Xeloda)	1998	Breast cancer	Full approval
Liposomal doxorubicin (Doxil)	1999	Ovarian cancer	Full approval
Temozolomide (Temodal)	1999	Anaplastic astrocytoma	Full approval
Denileukin diftitox (Ontak)	1999	Cutaneous T-cell lymphoma	Not yet upgraded
Liposomal cytarabine (DepoCyt)	1999	Lymphomatous meningitis	Not yet upgraded
Celecoxib (Celebrex)	1999	Reduction of colonic polyps	Not yet upgraded
Gemtuzumab ozogamicin (Mylotarg)	2000	Acute myelogenous leukemia	Not yet upgraded
Alemtuzumab (Campath)	2001	Chronic lymphocytic leukemia	Not yet upgraded
Imatinib mesylate (Gleevec)	2001	Chronic myelogenous leukemia (CML)	Full approval
Imatinib mesylate (Gleevec)	2002	Gastrointestinal stromal tumor	Not yet upgraded
Ibritumomab tiuxetan (Zevalin)	2002	Low-grade non-Hodgkin's lymphoma	Not yet upgraded

Oxaliplatin (Eloxatin)	2002	Colon cancer	Full approval
Anastrozole (Arimidex)	2002	Breast cancer	Not yet upgraded
Imatinib mesylate (Gleevec)	2002	Newly diagnosed CML	Not yet upgraded
Imatinib mesylate (Gleevec)	2003	Higher dosage for CML	Not yet upgraded
Imatinib mesylate (Gleevec)	2003	Pediatric chronic myelogenous leukemia	Not yet upgraded
Gefitinib (Iressa)	2003	Non–small-cell lung cancer	Not yet upgraded
Bortezomib (Velcade)	2003	Multiple myeloma	Full approval
Tositumomab (Bexxar)	2003	Low-grade non-Hodgkin's lymphoma	Not yet upgraded
Cetuximab (Erbitux)	2004	Colon cancer	Recent approval
Pemetrexed (Alimta)	2004	Non–small-cell lung cancer	Recent approval
Letrozole (Femara)	2004	Breast cancer following tamoxifen therapy	Recent approval
Clofarabine (Clolar)	2004	Pediatric relapsed/refractory acute leukemia	Recent approval
Tositumomab (Bexxar)	2004	Expanded indication for low-grade non-Hodgkin's lymphoma	Recent approval

Table 1. Post-marketing status for accelerated approval oncology drugs, biologics, and supplemental applications 1995-2004.[311]

equivalent to receiving full approval. Because a drug receiving accelerated approval enjoys the same commercial access as a fully approved treatment, manufacturers lose their sense of urgency in completing studies. The fact that AstraZeneca completed the Iressa validation studies quickly, but then found negatively conclusive results, is likely to further disincentivize manufacturers from completing clinical studies. While pharmaceutical companies are unlikely to completely shirk due diligence requirements because of the potential harm to their reputations, there are several operational constraints that make it difficult for companies to rapidly fulfill their confirmatory trial obligations. First, validation study designs may be either too complex to

[311]Data based on information from Roberts and Chabner, supra note 6, at 503, Dagher et. al., supra note 107, at 1501-02, Accelerated Approvals – NDAs, Accelerated Approvals – NDA Supplements, supra note 131. See also, Appendix A.

carry out, or they may be randomized, placebo controlled studies. In the case of randomized clinical trials, desperate patients are unlikely to enroll if they know they may receive a placebo instead of a new cancer treatment.[312] Furthermore, randomized validation trials generate ethical concerns since physicians may have to violate the standard of care by enrolling dying patients in trials with the knowledge that some patients will not receive a treatment.[313] In some cases, validation trials may not proceed quickly due to enrollment hesitation brought on by the excessive toxicity of a drug.[314] Finally, in the rare circumstance, confirmatory trials may not get completed due to competition for patients with another drug on the market or concurrent clinical studies of a competitor drug intended to treat the same disease.[315]

Long delays in finishing confirmatory trials can have several negative impacts. First, from a patient perspective, confirmatory trials are necessary to establish definitive proof of safety and efficacy for a drug that is likely being used to save lives. Taking costly, toxic, and ineffective drugs inordinately harms patients, especially if another treatment is available. Second, if sponsors take a long time to finish confirmatory trials, that means that secondary trials to study different doses, indications, and pharmacokinetics in specific populations are not likely to even get started. Third, if accelerated approval drugs are on the market under the assumption they have some efficacy, then perhaps the research and development of truly effective treatments is also delayed. The faster an accelerated drug is shown to be effective or ineffective, the more pressure there is to develop a better or actually effective alternative.

[312]Edward Susman, *Accelerated Approval Seen as Triumph and Roadblock for Cancer Drugs*, Journal of the National Cancer Institute, Oct. 20, 2004, at 1495.
[313]See *FDA Oncologic Drugs Advisory Committee Meeting*, Mar. 13, 2003, at 169 (statements of Dr. Donna Przepiorka, Chair of ODAC).
[314]Id.
[315]Id.

The current public backlash against the FDA provides the agency and ODAC the political power to bolster regulations surrounding confirmatory trials. Some observers have proposed making it mandatory for companies to have confirmatory trials ongoing at the time of accelerated approval, or to make accelerated approval decisions at an interim point of a larger, ultimately confirmatory trial.[316] While this would make the completion of validation trials much more likely, there are significant operational and enrollment issues in developing a larger trial (particularly with rarer cancers) that could delay getting patients access to a promising therapy. The FDA has also flirted with the idea of implementing an accelerated approval model similar to one used in approving AIDS treatments.[317] The AIDS model typically has two randomized trials with 1,000 patients.[318] The surrogate endpoint of viral load after 24 weeks is used to provide evidence for accelerated approval.[319] Full approval is then obtained using the same study by demonstrating the effect on the same endpoint after 48 weeks.[320] Unfortunately, the majority of accelerated approvals for cancer drugs were based on studies that were either uncontrolled or compared two dose levels and did not use an active comparator.[321] Additionally, the AIDS model also runs into questionable ethical grounds if the randomized studies utilize a placebo. As a result, the AIDS model may not be practical for most experimental cancer drugs, or may expose cancer patients to unnecessary risk through placebo controlled studies.

Any reform dealing with confirmatory trials for accelerated approval drugs needs to facilitate the acceleration of important life-saving drugs to market and ensure that pharmaceutical companies have the proper incentives to complete validation trials. Since most accelerated approval products are also fast-track designated drugs,

[316]See Susman, supra note 312, at 1495; see also *FDA Oncologic Drugs Advisory Committee Meeting*, Mar. 12, 2003, at 15, 25 (statements of Dr. Richard Pazdur, FDA Division of Oncology Drug Products).
[317]Id.
[318]Id.
[319]Id.
[320]Id.
[321]See Dagher et al, supra note 107, at 1500.

conversations regarding confirmatory trials as a part of a comprehensive development program need to integrated into formal sponsor-FDA consultations as early as possible. Pharmaceutical companies and the FDA should work together to determine plans on dealing with post-marketing study enrollment, timely execution of trials, potential problems with confirmatory trials, and also alternative trial designs if the initial designs fail. Specific requirements could be formalized as part of the fast-track guidance, or perhaps implemented as a modified special protocol assessment (SPAs). SPAs are a binding agreement between the FDA and a sponsor on a study protocol, and they may be useful in forcing diligence and collaboration between the agency and a pharmaceutical company on validation studies.[322] Another method to incentivize companies to conduct confirmatory trials at the time of approval would be to include validation trial plans as a formalized element of accelerated drug approvals. While the ODAC may currently informally consider post-marketing development plans in deciding whether to grant Subpart H approval, a codified decision criteria may force pharmaceutical companies to develop more robust validation trial plans earlier. Additionally, in order to respect the significant operational concerns in creating larger scale trials, perhaps the agency could set up a default rule where confirmatory trials would need to be ongoing at the time of accelerated approval unless a pharmaceutical company successfully petitions the FDA. This would compel pharmaceutical companies to think about confirmatory trials at an early stage, but also give the FDA flexibility in granting accelerated approval to important drugs like Clolar that do not have planned trials at the time of application.

While these changes to the approval process for cancer drugs are likely to be met with opposition from the cancer community, the current public backlash against the FDA and calls for more widespread reforms may make these incremental changes more palatable. Cancer patient advocates should also realize that these reforms are unlikely to discourage the ODAC and the FDA from using fast-track and accelerated approval for

[322] 21 USC § 355(b)(4).

oncology drugs. Defining a clear response for when confirmatory trials fail, and also providing incentives for pharmaceutical companies to be diligent in conducting confirmatory trials will ultimately ensure that cancer patients exercise their personal autonomy to choose from among the best and most effective accelerated oncology treatments.

Conclusion

The FDA drug approval processes have come a long way since the days of protecting the public from snake oil salesmen. AIDS and cancer activists have toiled for years to force liberalization of FDA regulations, and as a result, the U.S. has been rewarded with strong safety and efficacy standards for drugs and also compassionate exemptions to save terminally ill patients. Looking at the empirical analyses, the fast-track programs and accelerated approval regulations are clearly valuable tools in providing access and expediting commercialization of innovative, life-saving treatments. Any risk of curtailing these gains is, without question, a considerable concern for anyone with a life-threatening disease.

Over the years, the FDA has sporadically endured episodes of bad press, but the recent controversies have created an unprecedented swell of negative public opinion of the FDA. Consequently, the agency has already started to succumb to public and political pressures by introducing new bureaucratic elements to drug approval and safety monitoring procedures. Despite the pressure on the agency to reform, a response to the public backlash against the FDA is unlikely involve draconian changes that will significantly impact the acceleration of oncology drug approvals. Unfortunately, the cancer community suddenly perceives a growing conservative trend that threatens to undo the years of work spent convincing the FDA that the agency

needs to expedite the approval of life-saving oncology drugs. However, the perception that the FDA and the ODAC are reverting to a more conservative approval viewpoint appears to be a construct perpetrated by media doomsayers, financial analysts, and worried cancer activists. Not only has the FDA continued to apply the same risk/benefit calculus to oncology drugs, but the agency has also granted accelerated approval and fast-track designation to several experimental drugs in the midst of the recent controversies. While cancer patients claim that more restrictive approval policies will violate their personal autonomy, any potential tightening of regulations by the FDA and ODAC will likely serve to improve the development of information critical to making medical decisions.

For years, the ODAC has recognized a need to tweak the accelerated approval mechanisms to incentivize pharmaceutical companies to complete important post-marketing validation studies. Combined with the first occurrence of an accelerated approval oncology drug with negative confirmatory studies, calls for reform of the FDA's drug approval policies provide the agency with an excellent opportunity to embrace the winds of change and implement stronger regulations of post-marketing studies. The recommendations in this paper will help generate more rigorous clinical trial data to aid cancer patients in exercising their personal autonomy and also enable the FDA to fulfill its mandate and protect some of society's most vulnerable members from unsafe and ineffective drugs.

Appendix A. Accelerated Approval and Fast-Track Oncology Drugs as of March 2005

Oncology Drugs Granted Accelerated Approval

Drug or Biologic Agent (Trade Name)	Company	Approval Indication	Fast Tracked	NDA/BLA Filed	Priority Review	Approved	Status
Dexrazoxane (Zinecard)	Pharmacia	Reduction of doxorubicin toxicity	n/a	Aug-94	Yes	May-95	Full approval
Liposomal doxorubicin (Doxil)	Ortho Biotech	Kaposi's sarcoma	n/a	Sep-94	Yes	Nov-95	Not yet upgraded
Amifostine (Ethyol)	Medimmune	Reduction of cisplatin toxicity	n/a	Feb-96	Yes	Mar-96	Not yet upgraded
Docetaxel (Taxotere)	Sanofi-Aventis	Breast cancer	n/a	Jul-94	Yes	May-96	Full approval
Irinotecan (Camptosar)	Pfizer	Colon cancer	n/a	Dec-95	Yes	Jun-96	Full approval
Capecitabine (Xeloda)	Roche	Breast cancer	n/a	Oct-97	Yes	Apr-98	Full approval
Denileukin diftitox (Ontak)	Ligand Pharma	Cutaneous T-cell lymphoma	n/a	Dec-97	Yes	Feb-99	Not yet upgraded

Liposomal cytarabine (DepoCyt)	Skye Pharma	Lymphomatous meningitis		Oct-98	Yes	Apr-99	Not yet upgraded
Liposomal doxorubicin (Doxil)	Ortho Biotech	Ovarian cancer		Dec-98	Yes	Jun-99	Not yet upgraded
Temozolomide (Temodal)	Schering	Anaplastic astrocytoma		Aug-98	Yes	Aug-99	Full approval
Celecoxib (Celebrex)	Pfizer	Reduction of colonic polyps		Jun-99	Yes	Dec-99	Not yet upgraded
Gemtuzumab ozogamicin (Mylotarg)	Wyeth	Acute myelogenous leukemia		Oct-99	Yes	May-00	Not yet upgraded
Alemtuzumab (Campath)	Genzyme	Chronic lymphocytic leukemia	Oct-98	Dec-99	Yes	May-01	Not yet upgraded
Imatinib mesylate (Gleevec)	Novartis	Chronic myelogenous leukemia	Jul-99	Feb-01	Yes	May-01	Full approval
Imatinib mesylate (Gleevec)	Novartis	Gastrointestinal stromal tumor		Oct-01	Yes	Feb-02	Not yet upgraded
Ibritumomab tiuxetan (Zevalin)	Biogen Idec	Low-grade non-Hodgkin's lymphoma (NHL)	Jun-00	Nov-00	Yes	Feb-02	Not yet upgraded
Oxaliplatin (Eloxatin)	Sanofi-Aventis	Colon cancer	May-02	Jun-02	Yes	Aug-02	Full approval
Anastrozole (Arimidex)	AstraZeneca	Breast cancer	Dec-01	Mar-02	Yes	Sep-02	Not yet upgraded
Imatinib mesylate (Gleevec)	Novartis	Newly diagnosed chronic myelogenous leukemia		Jun-02	Yes	Dec-02	Not yet upgraded
Imatinib mesylate (Gleevec)	Novartis	Higher dosage for chronic myelogenous leukemia		Dec-02		Apr-03	Not yet upgraded
Gefitinib (Iressa)	AstraZeneca	Non–small-cell lung cancer	Oct-99	Aug-02	Yes	May-03	Not yet upgraded
Bortezomib (Velcade)	Millennium	Multiple myeloma	May-02	Jan-03	Yes	May-03	Full approval
Imatinib mesylate (Gleevec)	Novartis	Pediatric chronic myelogenous leukemia		1-Jun		May-03	Not yet upgraded
Tositumomab (Bexxar)	Corixa /GSK	Low-grade non-Hodgkin's lymphoma	Nov-98	Sep-00	Yes	Jun-03	Not yet upgraded

Cetuximab (Erbitux)	ImClone/BMS	Colon cancer	Feb-01	Aug-03	Yes	Feb-04	Recent approval
Pemetrexed (Alimta)	Eli Lilly	Non–small-cell lung cancer	Jul-03	Nov-03	Yes	Aug-04	Recent approval
Letrozole (Femara)	Novartis	Breast cancer following tamoxifen therapy		Apr-04	Yes	Nov-04	Recent approval
Clofarabine (Clolar)	Bioenvision/Genzyme	Pediatric relapsed/refractory acute leukemia	Sep-03	Mar-04	Yes	Dec-04	Recent approval
Tositumomab (Bexxar)	Corixa /GSK	Expanded indication for low-grade NHL		Jul-04	Yes	Dec-04	Recent approval

Oncology Drugs That Have Requested Accelerated Approval

Drug or Biologic Agent (Trade Name)	**Company**	Approval Indication	**Fast Tracked**	**NDA/BLA Filed**	**Priority Review**	**Status**
INGN201 (Advexin)	Introgen Therapeutics	Head and neck cancer	Sep-03	Dec-04		PIII
Decitabine (Dacogen)	SuperGen Inc	Myelodysplastic syndromes	May-03	Nov-04		PIII
Efaproxyn (RSR13)	Allos Therapeutics	Brain metastases originating from breast cancer	Nov-00	Feb-04	Yes	"Approvable" letter (6/2/04), need PIII data
Sphingosomal vincristin (Marqibo)	Inex Pharma	Relapsed, aggressive non-Hodgkin's lymphoma	Aug-00	Mar-04		Not approvable Dec-04, PII

Oblimersen sodium (Genasense)	Genta Inc.	Advanced malignant melanoma	Oct-99	Dec-03	Yes	ODAC rejected in May-04, PIII

Oncology Drugs Granted Fast-Track Designation Only

Drug or Biologic Agent (Trade Name)	**Company**	Approval Indication	**Fast Tracked**	**NDA/BLA Filed**	**Priority Review**	**Approved**	**Status**	
RC-1291	Rejuvenon	Cachexia and anorexia in cancer patients	Feb-05				PII	
Phenoxodiol	Novogen	Prostate cancer	Jan-05				PIb/IIa	
Prochymal	Osiris Therapeutics	Graft v. host problems in cancer patients	Jan-05				PII	
AMG 706	Amgen	Gleevec-resistant gastrointestinal stromal tumors	Dec-04				PII (2/05)	
HuMax-CD20	Genmab AS	Chronic lymphocytic leukemia	Dec-04				Pi/II (2/05)	

TTS CD3	Active Biotech AB	Non–small-cell lung cancer	Dec-04				PI (2/05)
CG53135	CuraGen	Hematopoietic stem cell trans-plan-ta-tion	Dec-04				PII
Phenoxodiol	Novogen	ovarian cancer	Nov-04				PIII (4/10/05)
Glufosfamide	Threshold Pharma	Pancreatic cancer	Nov-04				PIII
Bortezomib (Velcade)	Millennium	Mantle cell lymphoma	Nov-04				PII
VEGF Trap	Regeneron/Sanofi	Niche cancer indication	Oct-04				Pi/II (1/05)
FK228	Gloucester Pharma	T-cell lymphoma	Oct-04				PII
MDX-010/MDX-1379	Medarex	Metastatic melanoma	Oct-04				PIII
L-BLP25	Biomira / Merck KGaA	Non–small-cell lung cancer	Sep-04				PIIb
CCI-779	Wyeth	Advanced renal cell carcinoma	Aug-04				PIII
Pixantrone	Cell Therapeutics Inc	Relapsed, aggressive non-Hodgkin's lymphoma	Jul-04				PIII
Tipifarnib (Zarnestra)	Johnson & Johnson	Acute myeloid leukemia	Jun-04	Jan-05			PIII
BAY 43-9006	Bayer/Onyx Pharma.	Metastatic renal cell carcinoma	Apr-04				PIII (3/12/05)
Motexafin gadolinium (Xcytrin)	Pharmacyclics	Brain metastases in non-small cell lung cancer patients	Dec-03				PIII (3/15/05)
GW 572016	GlaxoSmithKline	Metastic breast cancer	Dec-03				PIII
Telcyta	Telik Inc	Non–small-cell lung cancer	Dec-03				PIII
MLN2704	Millennium	Prostate cancer	Dec-03				PI/II, in FDA Pilot Program 2

Oncology Drugs Granted Fast-Track Designation Only (continued)

Drug or Biologic Agent (Trade Name)	Company	Approval Indication	Fast Tracked	NDA/BLA Filed	Priority Review	Approved	Status
Nelarabine	GlaxoSmithKline	T-cell acute lymphoblastic leukemia	Dec-03	Mar-05			
Paclitaxel (Tocosol)	Sonus Pharma	Bladder cancer	Oct-03				PIIb (3/18/05)
Azacitidine (Vidaza)	Pharmion	Myelodysplastic syndrome	Oct-03	Dec-03		May-04	Approved
Provenge	Dendreon	Prostate cancer	Sep-03				PIII (3/30/05)
Satraplatin	GPC Biotech	Prostate cancer	Sep-03				PIII (3/30/05)
Telcyta	Telik Inc	Ovarian cancer	Sep-03				PIII
Avastin	Genentech	Colon cancer	Jul-03	Sep-03	Nov-03	Feb-04	Approved
Combrestatin A4P (CA4P)	OXiGENE Inc.	Thyroid cancer	Jun-03				PII
Oblimersen sodium (Genasense)	Genta Inc.	Chronic lymphocytic leukemia	Jun-03				PIII met primary endpts
Paclitaxel poliglumex (Xyotax)	Cell Therapeutics Inc	Non–small-cell lung cancer	Jun-03				PIII
Revlimid	Celgene	Myelodysplastic syndrome	Apr-03				PI/II
Revlimid	Celgene	Multiple myeloma	Feb-03				PIII
Onconase	Alfacell	Malignant mesothelioma	Feb-03				

Insegia	Aphton	Gastric cancer	Feb-03				PIII
Tariquidar	QLT Inc.	Non–small-cell lung cancer	Oct-02				PIII stopped
Insegia	Aphton	Pancreatic cancer	Sep-02				PIII did not meet primary endpts
Abraxane	American Bio-Science	Breast cancer	Jan-03	May-04	Std Rev	Jan-05	Approved
Canvaxin	CancerVax	Advanced stage melanoma	Jan-03				PIII
Rubitecan (Orathecin)	SuperGen Inc	Pancreatic cancer	Nov-02	Jan-04			Withdrew NDA Jan-05
Virulizin	Lorus Thera-peutics	Pancreatic cancer	Jun-02				PIII (3/13/05)
Pemetrexed (Alimta)	Eli Lilly	Malignant pleural mesothelioma	Jun-02	Sep-03		Feb-04	Approved
MLN518	Millennium	Acute Myeloid Leukemia	Jun-02				PI/II
Erlotinib (Tarceva)	OSI Pharma	Non-Small Cell Lung Cancer - Front Line	May-02				PIII
Erlotinib (Tarceva)	OSI Pharma	Non-Small Cell Lung Cancer - 2nd/3rd Line	Sep-02	Jul-04	Sep-04	Nov-04	Approved, in FDA Pilot Prog 1
Bortezomib (Velcade)	Millennium	Multiple myeloma	May-02	Sep-04	Dec-04	Mar-05	Approved
IL13-PE38QQR	NeoPharm	Brain cancer	May-02				PIII, in FDA Pilot Program 2
Exisulind (Aptosyn)	OSI Pharma	Non–small-cell lung cancer	May-02				PIII, did not meet primary endpts
Temsirolimus (CCI-779)	Wyeth	Renal cell carcinoma	Mar-02				PIII
Oncophage	Antigenics Inc.	Metastatic melanoma	Feb-02				PIII

Oncology Drugs Granted Fast-Track Designation Only (continued)

Drug or Biologic Agent (Trade Name)	Company	Approval Indication	Fast Tracked	NDA/BLA Filed	Priority Review	Approved	Status
Cotara	Peregrine Pharma	Recurrent glioblastoma multiforme	Oct-01				PIII
Oblimersen sodium (Genasense)	Genta Inc.	Multiple myeloma	Sep-01				PIII, not meet primary endpts
Atrasentan (Xinlay)	Abbott Labs	Prostate cancer	Mar-01	Dec-04			PIII
Protegrin 1B-367 Rinse	Intrabiotics	Chemotherapy-Induced Ulcerative Oral Mucositis	Jan-01				PII failed - Terminated Sep-02
Affinitak	ISIS Pharma	Non-Small Cell Lung Cancer	Nov-00				PIII failed - Prob. Terminated
Theratope	Biomira Inc.	Breast cancer	May-00				PIII failed - Co-dev abandoned
Nolatrexed dihydrochloride (Thymitaq)	Eximias Pharma	Unresectable hepatocellular carcinoma	Apr-00				

Tavocept	BioNumerik Pharma	Prevent nerve and kidney damage caused by cancer therapies	Mar-00				PIII
Arsenic trioxide (Trisenox)	Cell Therapeutics	Acute promyelocytic leukemia	Feb-00	Mar-00		Sep-00	Approved
IL-4 Fusion Toxin	Neurocrine Biosciences	Glioblastoma Multiforme	Oct-99				PII failed - Terminated Feb-03
IntraDose Injectable Gel	Matrix Pharma (Chiron)	Recurrent Head and Neck Cancer	May-99	Jan-01	No	Not Approvable (Nov-01)	PIII failed - Prob. Terminated
Foscan	Scotia Pharma	Head and Neck cancer	Mar-99	Oct-99	No	Not Approvable (Sep-00)	PIII
Docetaxel (Taxotere)	Sanofi-Aventis	Non–small-cell lung cancer	Feb-99	Jun-99	Yes	Dec-99	Approved
Ovarex Mab	ViRexx	Ovarian Cancer	Dec-98				PIII
Exisulind (Aptosyn)	OSI Pharma	Familial Adenomatous Polypsis	Jul-98	Aug-99	No	Not Approvable (Sep-00)	PII failed - Terminated
Trastuzumab (Herceptin)	Genentech	Breast cancer	Mar-98	May-98	Yes	Oct-98	Approved