

# Second Thoughts: Do the FDA's Responses to a Fatal Drug Trial and the AIDS Activist Community's Doubts About Early Access to Drugs Hint at a Shift in Basic FDA Policy?

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## I. INTRODUCTION

On June 25, 1993, forty-four year-old Howard Tichenor was rushed into a hospital emergency room in Fredericksburg, Virginia, suffering from multiple organ failure. His liver had ceased functioning, sending his body into shock and causing his other organs to "fall like dominoes."<sup>1</sup> He also was suffering from lactic acidosis, a rare but potentially fatal accumulation of waste materials in the cells.<sup>2</sup> Jay Hoofnagle, a physician at the National Institutes of Health (NIH) had been following Tichenor as part of an NIH-run clinical trial of fialuridine (FIAU), a promising new drug for treatment of the hepatitis B virus.<sup>3</sup> For Hoofnagle, the finding of lactic acidosis (which also had afflicted another patient in a prior trial of the drug) "struck like a lightning bolt," for it made him realize his mistake in disregarding earlier less serious problems experienced by other participants in the FIAU study.<sup>4</sup> The next day, Hoofnagle began contacting the fourteen other persons enrolled in the drug trial, and told them to cease taking FIAU immediately. Tichenor underwent a liver transplant on July 4th and died five days later, his body overwhelmed by the acidosis.<sup>5</sup> By the end of August 1993, two other persons in the NIH clinical trial had undergone liver transplants as a result of the drug's effects and four more subjects had died, killed by the drug once touted as "a miracle cure for hepatitis B."<sup>6</sup>

Several months after Dr. Hoofnagle terminated the FIAU trial, a group of AIDS treatment activists wrote a memo to Food and Drug Administration (FDA) Commissioner David Kessler urging him to establish an advisory committee to discuss "the broader impact of accelerated approval on trial design and drug development," and to address discouraging data on FDA-approved anti-AIDS drugs.<sup>7</sup> Several weeks earlier, members of New York's Treatment Action Group (TAG), an AIDS activist organization that had broken off from the more radical AIDS Coalition to Unleash Power (ACT-UP)<sup>8</sup>, had argued that recent changes in FDA regulations had allowed AIDS drugs on

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<sup>1</sup> Larry Thompson, *The Cure That Killed*, DISCOVER MAG., Mar. 1994, at 56.

<sup>2</sup> John Schwartz, *And Then the Patients Suddenly Started Dying*, WASH. POST, Sept. 7, 1993, at 1.

<sup>3</sup> See *infra* pt. III.

<sup>4</sup> Schwartz, *supra* note 2.

<sup>5</sup> Thompson, *supra* note 1.

<sup>6</sup> Associated Press, *5th Patient Dies in Testing a Drug*, N.Y. TIMES, Sept. 1, 1993, at 11.

<sup>7</sup> *FDA Should Establish Committee to Discuss Impact of Accelerated Approval on AIDS Drug Development*, F-D-C REP. ("The Blue Sheet"), Jan. 26, 1994, at 10.

<sup>8</sup> Laurie Garrett, *Battle on AIDS Drugs*, NEWSDAY, Sept. 6, 1994, at 4.

the market without a clear demonstration of their clinical benefits, and partially blamed the failure to make a breakthrough in the war on AIDS on "poor drugs, in poor trials, poorly analysed."<sup>9</sup>

At first glance the stories appear unrelated, but closer examination reveals a common significance between the FIAU trial and the developing rift in the formerly unified ranks of AIDS activists. Both events have influenced recent FDA policy. As a direct result of the FIAU tragedy, the FDA has proposed rules designed to prevent the recurrence of such devastating drug trials by requiring more rigorous reporting of adverse experiences associated with human drug experiments.<sup>10</sup> Since early 1994, several prominent figures in the AIDS research and patient activist communities have expressed their reservations with the haphazard testing of AIDS drugs, voiced their strong disapproval (with increasing unity and effectiveness) of the notion of flooding the market with unproven "remedies,"<sup>11</sup> and found the FDA to be an attentive audience.

The regulations proposed in the aftermath of the FIAU clinical trial and the call of some AIDS activists for a reexamination of accelerated approval and for more rigorously controlled tests of anti-AIDS drugs are important developments. They each exemplify apprehension toward the FDA's recent tendency to relax the drug approval processes. This change in perspective may have significant ramifications for the ability of persons to access the medical "treatment" of their choice.<sup>12</sup>

In contrast to these trends (which together suggest a more active role for the FDA) there remain powerful forces united against efforts to unduly burden the public's access to a wider spectrum of drug treatment options. The pharmaceuticals industry, traditional AIDS activists, and Congress have each sought to minimize any steps that would impair their goals of reducing regulation, and continuing the trend toward broader access to drugs earlier in the development processes.<sup>13</sup>

This article argues that while the calls for re-evaluation of accelerated approval and the consequences of the FIAU clinical trials illustrate significant, legitimate concerns with the way the FDA regulates the testing and marketing of drugs, it by no means appears that the thoughtful criticisms surrounding these events represent the first wave of a comprehensive attack on the FDA's recent trend toward facilitating early access to drugs. On the contrary, the proposed regulations have come under strong criticism during their public comment period, and may well be subject to substantial revision by the FDA before their final adoption; they nearly were rendered moot as a result of a threatened congressional moratorium on many new federal regulations.<sup>14</sup> In addition, the advocates of strengthened, expanded accelerated approval of new drugs will likely find their position in ascendance on Capitol Hill, despite the important inroads made by TAG to prompt closer evaluation of accelerated approval's possible drawbacks. Furthermore, no matter the ultimate outcome of the proposed rulemaking and the eventual development of drug approval policy, this article argues that the FDA's recent successes in speeding the investigation and approval of new drugs should not be undermined or reversed in any significant fashion. Rather, the FDA and Congress should seek to ex-

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<sup>9</sup> *AIDS Drugs*, *ECONOMIST*, Jan. 8, 1994, at 79.

<sup>10</sup> See Adverse Experience Reporting Requirements for Human Drugs and Licensed Biological Products, 59 Fed. Reg. 54,046 (Oct. 27, 1994) (to be codified at 21 C.F.R. §§ 20, 310, 312, 314, and 600); See also *infra* pts. IV, V.

<sup>11</sup> See *infra* pt. III.

<sup>12</sup> *Id.*

<sup>13</sup> See *infra* pt. VI.

<sup>14</sup> See *infra* pts. V, VI.

pand these successes, and the legislative and regulatory provisions that made them possible, while continuing to take particular care to consider the well-being of human subjects throughout the clinical trials process.

Part II examines the progression from the Supreme Court's 1979 decision upholding the FDA's right to ban interstate distribution of the claimed (though unapproved) cancer remedy Laetrile,<sup>15</sup> through the development of the current scheme of regulations that greatly has expanded early access to more drugs. Part III addresses recent developments and disputes on the proper direction for AIDS research and clinical investigations. Part IV details the FIAU incident and discusses the impact the tragedy may have on future drug development and testing. Part V addresses the FDA's newly-proposed rules and analyzes them in light of the public comments thereto. Part VI examines likely future directions in drug availability, viewed in light of volatile scientific, clinical, and political climates.

## II. BACKGROUND

From the 1970s through the early 1980s, many Americans traveled to Mexico to obtain Laetrile (amygdalin), a substance derived from apricot pits that was claimed to be effective in fighting cancer.<sup>16</sup> Their journeys were necessitated by the FDA's history of enforcement actions against the illicit substance and its marketers, which dated back to the 1920s and had continued through seizures in Dallas, Texas, in 1960.<sup>17</sup> In 1975, terminally-ill cancer patients sued to enjoin the FDA from interfering with the interstate shipment of Laetrile.<sup>18</sup> The Federal Food, Drug, and Cosmetic Act (FDCA),<sup>19</sup> however, prohibited interstate shipment of any "new drug" until government approval of a new drug application (NDA) supported by substantial proof of safety and effectiveness in the form of adequate, well-controlled studies.<sup>20</sup> The Commissioner of Food and Drugs had never determined that Laetrile was "generally recognized . . . as safe and effective" for *any* uses.<sup>21</sup> Before the case reached the Supreme Court, the district and circuit courts had made several statutory and constitutional findings, each based on tenuous judicial logic.<sup>22</sup>

A unanimous Supreme Court upheld the FDA's claimed power to block the interstate shipment of Laetrile on several grounds. Initially, the Court noted that "the [FDCA] makes no provision for drugs to treat terminally ill patients," and that there was no suggestion that Congress intended to protect only persons suffering from curable diseases.<sup>23</sup> The Court observed that for terminal patients, effectiveness need not be defined solely by capacity to cure, but could be measured by longer life or reduced pain. Furthermore, "the concept of safety . . . is not without meaning for terminal patients,"<sup>24</sup>

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<sup>15</sup> *United States v. Rutherford*, 442 U.S. 544 (1979).

<sup>16</sup> GEORGE J. ANNAS, JR., *STANDARD OF CARE* 136 (1993).

<sup>17</sup> See PETER B. HUTT & RICHARD A. MERRILL, *FOOD AND DRUG LAW: CASES AND MATERIALS* 557 (1991).

<sup>18</sup> *Rutherford*, 442 U.S. at 548.

<sup>19</sup> Pub. L. No. 75-717, 52 Stat. 1040 (1938), as amended 21 U.S.C. §§ 301 et seq. (1988).

<sup>20</sup> 21 U.S.C. §§ 321(p)(1), 355(d).

<sup>21</sup> 442 U.S. at 550.

<sup>22</sup> The trial court first determined on its own that Laetrile was safe and effective. The circuit court held that "the 'safety' and 'effectiveness' terms . . . have no reasonable application to terminally ill patients," and directed the FDA to promulgate regulations "as if" the drug had been found safe and effective. *Id.* at 548, 551 (citations omitted).

<sup>23</sup> *Id.* at 552.

<sup>24</sup> *Id.* at 555. In addition, a drug that is not inherently unsafe may become so by virtue of its ineffectiveness, if a patient consequently rejects conventional therapies in favor of the ineffectual "miracle" cure.

whose demises could be hastened by harmful drugs. In concluding, the Court refused plaintiffs' invitation to construe the FDCA to deny the Commissioner's authority over all drugs for terminally-ill patients, however toxic or ineffectual those drugs may be.<sup>25</sup>

The decision in *Rutherford* came down strongly on the side of benevolent government paternalism rather than personal autonomy, a holding that the Court noted was mandated by the text of the FDCA itself. In the years since that decision, however, largely in response to the AIDS epidemic,<sup>26</sup> the FDA has enacted several regulations that have removed certain impediments to access to experimental drugs, and focus more prominently on individual responsibility.<sup>27</sup>

As noted earlier, the FDCA generally prohibits shipment of unapproved new drugs in interstate commerce. The FDA, however, has the power to exempt from this prohibition those drugs intended "solely" for use in investigating their safety and effectiveness.<sup>28</sup> As one of the prerequisites to approving an NDA, the Secretary of Health and Human Services must then find, based on the results of the clinical investigations, that a new drug is safe and effective for its claimed use before allowing interstate shipment.<sup>29</sup> This process of testing the safety and effectiveness of new drugs begins with what is known as an investigational new drug application (INDA), and federal regulations define precise requirements for the phases of such trials.<sup>30</sup> Under current regulations, an INDA submitted to the FDA must contain a brief statement of the general investigational plan (including previous human experience with the drug, the estimated number of patients to be enrolled, and anticipated risks of particular severity), protocols of each planned study, manufacturing and control information, pharmacology data, and toxicology data based on animal or *in vitro* studies.<sup>31</sup> The clinical investigation of an untested drug generally is divided into three phases, which are usually sequential, but may overlap. Phase I studies are small (twenty to thirty subjects), closely monitored trials, and act as early indicators of the drug's metabolism, and pharmacologic and side effects. Phase II tests are well-controlled, closely monitored clinical studies designed to evaluate a drug's effectiveness. They typically enroll no more than several hundred subjects. Phase III includes expanded controlled and uncontrolled tests performed after obtaining preliminary evidence of effectiveness. The tests in this phase are intended to gather additional information of safety and effectiveness to aid in analyzing the drug's overall benefit-risk relationship.<sup>32</sup>

On June 22, 1987, new regulations came into effect allowing availability of promising investigational new drugs (INDs) for treatment use by patients with "serious and immediately life-threatening diseases for which no comparable or satisfactory alternative drug or other therapies exist."<sup>33</sup> In an effort to curtail health fraud and the marketing of "cures" of dubious medical value, treatment INDs are approvable only when the drug is currently undergoing (or has completed) clinical trials, and the sponsor is ac-

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<sup>25</sup> *Id.* at 557-58.

<sup>26</sup> See HUTT & MERRILL, *supra* note 17, at 552 (1991) (AIDS, first recognized in the late 1970s, attacks the body's immune system leaving it open to infections, cancer, and other diseases. AIDS initially spread rapidly in the homosexual community. AIDS activists' persistence "has brought about a revolution in the availability" of investigational and approved new drugs to treat AIDS).

<sup>27</sup> See *infra* notes 33, 41, 46 and accompanying text.

<sup>28</sup> 21 U.S.C. § 355(i).

<sup>29</sup> *Id.* § 505(b)(1)(A).

<sup>30</sup> See generally 21 C.F.R. § 312 (1995).

<sup>31</sup> *Id.* § 312.23.

<sup>32</sup> Descriptions of the INDA phases are found at 21 C.F.R. § 312.21.

<sup>33</sup> 52 Fed. Reg. 19,466 (May 22, 1987) (codified at 21 C.F.R. § 312.34).

tively pursuing market approval of the IND with "due diligence."<sup>34</sup> In promulgating the regulations, the FDA emphasized its belief that "[b]ecause of the different risk-benefit considerations involved in treating such diseases, . . . there needs to be a separate standard for drugs intended to treat immediately life-threatening diseases,"<sup>35</sup> and thus created the distinction the *Rutherford* Court had noted was missing from the FDCA. Now those suffering from life-threatening diseases can gain access to drugs for treatment use as early as the drug's Phase II trials. Furthermore, by loosening the requirement of showing efficacy, the FDA has made it easier for desperately ill patients to obtain a treatment IND.<sup>36</sup>

Comments to the proposed rule argued that the FDA did not have authority to promulgate rules allowing for treatment use (as opposed to investigational use) of new drugs.<sup>37</sup> The FDA's claim that it had power to authorize treatment INDs is debatable because the FDCA exempts from the interstate commerce prohibition only those drugs whose shipment is intended solely for purposes of investigating their safety and effectiveness,<sup>38</sup> and makes no explicit provision for treatment use. The FDA rejected this contention, however, citing its broad power to regulate clinical trials and stressing that treatment INDs can serve a useful function in investigating a drug's safety and efficacy.<sup>39</sup> The FDA also stressed that the treatment IND regulations contain ample protections for terminally ill patients (such as the requirements for informed consent, the availability for continued review of the treatment IND protocol by hospitals' Institutional Review Boards, and that the sponsor actively seek marketing approval), and thus were not inconsistent with *Rutherford*, which had emphasized the importance of carefully regulating drugs not yet proven to be safe and effective.<sup>40</sup>

Similarly, in 1988 the FDA approved regulations establishing procedures "designed to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses."<sup>41</sup> Recognizing that "physicians and patients are generally willing to accept greater risks or side effects from products that treat [such conditions]," the FDA stated it would exercise broad flexibility in analyzing and reviewing such investigational drugs.<sup>42</sup> The new procedures sought to encourage early consultation and cooperation between the FDA and sponsors in order to design optimal investigational studies. Furthermore, the FDA stated it would base its review for market approval on risk-benefit analysis, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy.<sup>43</sup> The significance of these regulations, however, remains questionable. AIDS activists viewed them as a political ploy, because they were promulgated (and made effective) in the

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<sup>34</sup> 21 C.F.R. § 312.34(b)(iii), (iv).

<sup>35</sup> 52 Fed. Reg. at 19,468. "Immediately life-threatening diseases" are those "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." *Id.*

<sup>36</sup> The FDA may deny treatment INDs for serious illnesses if there is insufficient evidence of safety and effectiveness; the requests of gravely ill patients may be denied only if there is no scientifically reasonable basis to believe the drug may be effective, or would not expose the patient to an unreasonable and significant additional risk of illness or injury. 21 C.F.R. § 312.34. In effect, there is a presumption that desperately ill patients will be able to obtain access to such drugs.

<sup>37</sup> 52 Fed. Reg. at 19,469.

<sup>38</sup> 21 U.S.C. § 355(i).

<sup>39</sup> 52 Fed. Reg. at 19,469.

<sup>40</sup> *Id.* at 19,471.

<sup>41</sup> 53 Fed. Reg. 41,516 (Oct. 21, 1988) (codified at 21 C.F.R. § 312.80-.88).

<sup>42</sup> 21 C.F.R. § 312.80.

<sup>43</sup> *Id.* §§ 312.82, 312.84.

midst of a presidential campaign.<sup>44</sup> Furthermore, the FDA's acknowledgment that the regulations were modeled on the development, evaluation, and approval of the first anti-AIDS drug zidovudine (AZT),<sup>45</sup> suggested that the regulations were superfluous, in that rapid development of new drugs could and did occur under the existing regulatory regime.

In late 1992, the FDA took yet another step in lowering barriers to drug approval with the enactment of regulations providing for accelerated approval of new drugs for serious or life-threatening illnesses.<sup>46</sup> These regulations allow the FDA to grant market approval for a new drug if adequate and well-controlled clinical trials show the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or an effect on a clinical endpoint other than survival or irreversible morbidity.<sup>47</sup> Accelerated approval remains contingent on the preparation of follow-up studies that verify and describe the drug's clinical benefit, where the relationship between the surrogate marker and the clinical benefit is uncertain.<sup>48</sup> The regulations further establish that approval may be withdrawn following a hearing if the postmarket studies fail to verify clinical benefits, or if the applicant does not pursue such studies "with due diligence."<sup>49</sup> In the context of AIDS drugs, the surrogate marker on which a drug's effect is evaluated is customarily a measure of the subject's CD4 cell count.<sup>50</sup> By March 1996, seven AIDS drugs had been approved under the regulations, but the FDA has come under increasing criticism from activist groups for its failure to compel drug manufacturers to prepare follow-up studies linking the surrogate markers with observed clinical benefits, as mandated by the regulations.<sup>51</sup> The FDA's failure to monitor the actual clinical course of a drug approved without the customary safeguards of adequate and well-controlled studies increases the possibility that such drugs are ineffective or even harmful.

### III. RECENT DEVELOPMENT AND DISPUTES ABOUT AIDS RESEARCH AND CLINICAL INVESTIGATIONS

Medical ethicist George Annas has observed that "AIDS politics has produced strange political allies," as pharmaceutical manufacturers, the Reagan and Bush administrations, and gay activist groups united in calling for deregulation of the drug approval process.<sup>52</sup> As the preceding section illustrates, this unlikely coalition has achieved some notable successes in reforming the FDA's procedures. Recently, however, fissures have developed within the AIDS activist community that have disrupted this once-united front, as some groups have pointedly questioned the scientific and ethical underpinnings of treatment INDs and accelerated approval. The mere suggestion, however, that the accelerated approval provisions may be flawed has drawn immediate, sharp criti-

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<sup>44</sup> ANNAS, *supra* note 16, at 139.

<sup>45</sup> 53 Fed. Reg. at 41,517.

<sup>46</sup> 57 Fed. Reg. 58,958 (Dec. 11, 1992) (codified at 21 C.F.R. § 314.510-.560).

<sup>47</sup> *Id.*

<sup>48</sup> 21 C.F.R. § 314.510.

<sup>49</sup> *Id.* § 314.530(a)(1),(2).

<sup>50</sup> Gina Kolata, *F.D.A. Debate on Speedy Access to AIDS Drugs Is Reopening*, N.Y. TIMES, Sept. 12, 1994, at 13. CD4 cells (T-cells) are white blood cells that are key components of the immune system. RANDY SHILTS, *AND THE BAND PLAYED ON* 42 (1987).

<sup>51</sup> See Kolata, *supra* note 50; see also Sally Lehrman, *AIDS Activists Urge Government to Go Slow in Clearing Unproven Drugs*, BIOTECHNOLOGY NEWSWATCH, Sept. 5, 1994, at 12 (activists charge that companies receiving quick approvals have failed to follow up with required studies that could clarify a drug's impact and most effective use).

<sup>52</sup> ANNAS, *supra* note 16, at 136.

cism. In August 1994, TAG questioned the validity of preliminary data supporting the accelerated approval application of the drug D4T, and shortly thereafter there appeared a scathing, anonymous ACT-UP pamphlet mockingly urging "JOIN TAG TODAY! Speak as a 'community representative' while destroying everything AIDS activists have fought and died for! . . . Be a conservative nihilist and . . . be 'smart,' cool, self-hating and GENOCIDAL."<sup>53</sup> While the pamphlet has an exceedingly harsh tone, it is nonetheless indicative of one of two fundamentally different ways to view drug trials and the regulation of new drugs.

Vast discrepancies in the perception of the value of widespread, early drug availability are evident in the medical community as well. Dr. Donald Abrams, a pioneer AIDS researcher, has commented that "[t]his idea that people have the right to have access to drugs that we're not sure work doesn't ring true . . ." <sup>54</sup> In an astonishingly stark contrast, a doctor who treats AIDS patients in Los Angeles told a TAG member that "[y]ou're being protected to death. There's a slaughter going on in this country every day . . . and we're worried about data?"<sup>55</sup> While there are powerful philosophical arguments in favor of the right to take drugs in the hope or belief that they might be beneficial, the Los Angeles physician's disregard of scientific reliability is disquieting.

TAG's calls for more thorough scientific investigation of proposed AIDS drugs come at a time when the AIDS research community is likewise changing its focus. A frustration with the slow progress in the fight against the AIDS virus has led to a growing consensus that "it is time to go back to the drawing board," that is, to fully learn general principles about the immune system and the way the AIDS virus attacks it.<sup>56</sup> In addition, researchers have observed with dismay HIV's ability to mutate and rapidly develop resistances to varied treatment methodologies.<sup>57</sup> One AIDS scientist has observed that "there's really an alphabet soup of mutations, induced by a wide variety of drugs,"<sup>58</sup> a sobering phenomenon that should give pause to those who advocate quick release of many anti-viral medications. This movement away from the search for a "quick fix" has made it more likely that the criticisms voiced by TAG and other groups will influence the way the FDA handles future drug investigation and approval.<sup>59</sup> Indeed, in September 1994, the FDA acknowledged as much by scheduling a meeting of the Antiviral Drugs Advisory Committee to discuss the future of accelerated approval.<sup>60</sup> Following the Committee's meeting, Commissioner Kessler reassured AIDS groups

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<sup>53</sup> Quoted in Garrett, *supra* note 8, at 4. See also Letter from TAG to David Barry, Vice Pres., Burroughs-Wellcome, regarding proposed drug protocols ("In general, we fear that the industry, taking advantage of the deregulation which the community helped to create, is increasingly abandoning the principles of clinical research"), quoted in *ICC Three-Drug Regimen Protocol's Lack of Randomization/Controls Concerns Advocacy Group*, F-D-C REP. ("The Blue Sheet"), June 1, 1994, at 6.

<sup>54</sup> David Brown, *Speedy Release of AIDS Drugs Challenged on Lack of Follow Through*, WASH. POST, Sept. 11, 1994, at 3.

<sup>55</sup> *Activists Decry Wait on Newest AIDS Drug*, THE RECORD, Sept. 13, 1994, at 11 (emphasis added) (Bergen Cty., NJ newspaper).

<sup>56</sup> See Sheryl Stolberg, *Seeking a Cure*, L.A. TIMES, Aug. 7, 1994, at 1 (detailing the establishment of the federal Office of AIDS Research as the central authority in the fight against AIDS, and a general plan to shift funding from clinical trials to basic research). This move away from emphasizing clinical research presumably will make it more difficult to enter such experiments.

<sup>57</sup> Laurie Garrett, *AIDS Drugs Meet Resistance*, NEWSDAY, Feb. 7, 1995, at B23.

<sup>58</sup> *Id.* (quoting Dr. Daniel Kuritzkes, Univ. of Colo.).

<sup>59</sup> See *TAG Seeks to Redefine Accelerated Approval*, 7 ANTIVIRAL AGENTS BULLETIN, Sept. 1994, available in NEXIS, Legal News library (noting that "TAG's . . . demands should be kept in perspective in that they represent a distinct, but vocal, minority in the . . . activist communities . . . TAG has been an opinion leader . . .").

<sup>60</sup> See Garrett, *supra* note 8.

that the FDA would carry out its oversight duties by demanding appropriate follow-up studies and withdrawing approval where changes in surrogate markers do not correlate with tangible clinical improvements.<sup>61</sup>

Despite this, the FDA did not accept TAG's most controversial proposal. The committee meeting had taken place during the emergence of protease inhibitors, a new class of AIDS drug that blocks replication of HIV at an earlier phase in cell reproduction than the approved drugs.<sup>62</sup> TAG had advocated that the FDA require a massive, placebo-controlled clinical trial, that would include an analysis of actual clinical outcomes and enroll 18,000 subjects (the largest U.S. AIDS drug trial), as a prerequisite for approving saquinavir (the first protease inhibitor).<sup>63</sup> At the meeting, supporters of TAG's proposal stressed their desire for "truly effective" drugs and treatment, and emphasized that "they and others may have to suffer or die in [such] trials in order for this to come about."<sup>64</sup>

Advocating such behavior in the interests of greater scientific advancement, while noble, is unlikely to attract a significant number of adherents,<sup>65</sup> and may run afoul of ethical standards if the control group receives a placebo or anything less than the best available treatment.<sup>66</sup> The TAG proposal also flies in the face of allowing greater drug availability, and it effectively would do away with the theory behind accelerated approval through the use of surrogate markers. As such, in light of the widespread support for accelerated approval and the recurrent insistence of many terminally ill patients that they have a right to the therapy of their choice, the prospects for large, simple trials for new AIDS drugs seem dim. Regrettably, participants at a recent AIDS conference have revealed recent studies that demonstrate that "even the much-ballyhooed protease inhibitors . . . are proving unable to kill HIV for more than a few months."<sup>67</sup>

A resolution of the dispute between advocates of unlimited access to drugs and those who favor more rigorous testing turns in part on the answers to several elemental questions: what constitutes meaningful autonomy, what is the proper role of the FDA in protecting the public, and what is the nature of individual rights in relation to the right of the rest of society to be protected from sham "remedies?" There appears to be tenable middle ground between an AIDS patient's statement in support of accelerated approval that "if some of us are willing to be guinea pigs, for God's sake, let us,"<sup>68</sup> and Professor Annas's view that, where the illness is fatal, "[c]onsent . . . seems a sham."<sup>69</sup> The FDA's current regulations on accelerated approval and treatment INDs seem capable of creating and preserving an equilibrium between access and consumer protection, as long as relevant safeguards are adhered to and violations are addressed.<sup>70</sup>

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<sup>61</sup> *FDA Looks to Fine-Tune Accelerated Approval Policy for AIDS Drugs*, 9 AIDS ALERT, Oct. 1994, at 135.

<sup>62</sup> Sally Lehrman, *Debate Heats Up Over Fast Drug Approval*, SAN FRANCISCO EXAMINER, Aug. 24, 1994, at 2.

<sup>63</sup> See Brown, *supra* note 54.

<sup>64</sup> See TAG *Seeks to Redefine Accelerated Approval*, *supra* note 59.

<sup>65</sup> See Garrett, *supra* note 8 ("people with AIDS can't afford to wait" (quoting Martin Delaney of Project Inform); "A Large Simple Trial of antivirals will crimp the pipeline . . . Too many of us just don't have the time for hard data" (quoting Brie Salzman of ACT-UP)).

<sup>66</sup> See, e.g., Kenneth J. Rothman & Karin B. Michels, *The Continuing Unethical Use of Placebo Controls*, NEW ENG. J. MED. 394 (Aug. 11, 1994).

<sup>67</sup> Garrett, *supra* note 57.

<sup>68</sup> Statement of Bill Roberts, *CNN News* (Sept. 13, 1994) (Cable News Network Television Broadcast).

<sup>69</sup> ANNAS, *supra* note 16, at 135 (citation omitted).

<sup>70</sup> See, e.g., 21 C.F.R. §§ 50.20 (general requirements for informed consent), 56 (institutional review boards), 312.32 (IND safety reports), 312.42 (clinical holds on INDs where human subjects are placed at unreasonable risk), 314.530 (withdrawal procedures for drugs licensed under accelerated approval), 314.80 (postmarketing adverse reaction reporting).

A consensus statement released by several AIDS organizations embodies a view that is harmonious with the workings of FDA regulatory procedures as they have evolved in recent years: “[p]eople with life-threatening illnesses have a fundamental right to choose the earliest possible access to new therapies which are reasonably safe *and which show significant promise of efficacy*.”<sup>71</sup> The requirement of reasonable safety embodies an effort to keep research subjects safe from actual harm, to the extent that researchers can guarantee such safety. By demanding at least a “significant promise” of efficacy, regulatory authorities have an additional means with which to protect the public by forbidding the marketing of elixirs that fail to attain even that lowered (but by no means minimal) standard.

The less that is known about the risks and benefits of an experimental drug or one that has received accelerated approval, the less meaningful is the decision whether to take such a drug.<sup>72</sup> However, AIDS treatment activists have noted the difficulty of maintaining patience in light of “the desperation we feel.”<sup>73</sup> Comprehensive FDA regulations protect AIDS patients who wish to gain entry into a clinical trial for a treatment IND rather than relying on existing treatments of limited efficacy. Among other things, these regulations require researchers to inform would-be subjects that the study involves research, identify all experimental procedures, describe reasonably foreseeable risks and expected benefits, disclose appropriate alternative procedures, explain who to contact in the event of injury, and remind the subject that participation is voluntary and may be discontinued at any time.<sup>74</sup> By faithfully adhering to these requirements, and others that it has promulgated, the FDA can expand access to promising therapies without compromising its function as consumer protector.

Annas has dismissed the ACT-UP slogan “A Drug Trial is Health Care Too” by stating “[o]f course, the truth is otherwise: a drug trial is research designed to test a hypothesis, not treatment meant to help individual patients.”<sup>75</sup> While this assertion is partially true, a proper application of the FDA’s regulations for treatment INDs and accelerated approval can minimize the differences between experimentation and therapy, with protections stemming from adequate preliminary and follow-up testing. Untoward results, however, can cast the research/therapy distinction in sharp relief: if an experiment does well “it was treatment; and if it [does] poorly or something [goes] wrong, it was an experiment.”<sup>76</sup> This observation neatly characterizes the FIAU debacle, which medical ethicist Arthur Caplan has described as a warning that “calls to weaken or eliminate FDA and other regulations about who gets experimental drugs should be viewed with great skepticism.”<sup>77</sup>

#### IV. THE FIAU INCIDENT

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<sup>71</sup> Statement of ACT-UP, Project Inform, and the San Francisco AIDS Foundation (emphasis added) (quoted in Garrett, *supra* note 8, at 4).

<sup>72</sup> See Brown, *supra* note 54 (quoting David Barr of Gay Men’s Health Crisis: “If there’s no information on how to use the drug effectively, . . . it’s a fairly empty choice.”).

<sup>73</sup> *Id.* See also *supra* text accompanying note 68.

<sup>74</sup> 21 C.F.R. § 50.25(a)(1)-(4), (7), (8) (emphasis added). In addition, FDA regulations do not preempt any other federal, state, or local informed consent laws requiring disclosure of more detailed information. *Id.* § 50.25(c).

<sup>75</sup> ANNAS, *supra* note 16, at 136.

<sup>76</sup> Lawrence K. Altman, *Fatal Drug Trial Raises Questions About “Informed Consent,”* N.Y. TIMES, Oct. 5, 1993, at C3 (quoting George J. Annas).

<sup>77</sup> Arthur Caplan, *A Question of Ethics in Drug Tests on Humans*, SACRAMENTO BEE, Sept. 16, 1993, at B7.

Hepatitis B is a chronically infectious disease that affects the liver, and afflicts approximately 300,000,000 people worldwide, including 1,000,000 persons in the United States. Like HIV, hepatitis B is transmitted sexually and via the transfusion of infected blood, although much more easily than HIV. Most persons infected with hepatitis B never get seriously ill, but may suffer from jaundice. In the United States, approximately 1500 people infected with hepatitis B will develop a lethal primary liver cancer annually, and another 5000 will develop cirrhosis of the liver.<sup>78</sup> Upon hearing of FIAU's promising initial testing, NIH scientists were enthused by the prospect of developing a new drug to combat the virus, which has resisted all treatment to date, with the exception of alpha interferon, an expensive, poorly tolerated drug of little efficacy.<sup>79</sup>

FIAU, first developed in the 1970s to treat herpes viruses, is one of a class of drugs known as nucleoside analogues, which closely resemble a component of DNA. Nucleoside analogues are designed to combat viruses by interfering with the virus' ability to replicate itself.<sup>80</sup> During the 1980s, the licensing rights to FIAU were transferred among three drug companies, as it had proven ineffective in treating different viruses in several tests. In 1990, however, two small NIH trials of FIAU on persons infected with both HIV and hepatitis B revealed marked inhibition of the latter virus. In 1992, Dr. Hoofnagle directed a month-long, twenty-four patient trial of FIAU on subjects with hepatitis B alone; six persons participating in the trial were cured with only minimal side effects.<sup>81</sup>

Encouraged by the prospects of developing an effective drug to combat hepatitis B, Eli Lilly & Co. (which had bought the rights to FIAU in August 1992) conducted promising animal toxicity studies and planned additional longer-term tests. The Hoofnagle trial began on March 24, 1993, tracking ten patients who had participated in the 1992 trial. Two months later, with the original subjects reporting few severe side effects, five more patients enrolled. Soon thereafter the subjects' side effect complaints of began to rise, and on June 10 one patient ceased taking his FIAU dosage. By June 25, the date Tichenor was presented at an emergency room with systemic organ failure and lactic acidosis, the subjects' complaints of crippling nausea; jaundice; peripheral neuropathy (painful tingling in the extremities); and muscle, kidney, and pancreatic damage had grown increasingly severe. Over the next two months, certain patients underwent futile liver transplants, and a total of five eventually died. It has been postulated that FIAU fatally damaged the subjects' mitochondria, structures within cells that produce the energy needed to keep the cell alive.<sup>82</sup>

News of the FIAU tragedy prompted immediate introspection, and a sense of "there but for the grace of God go I" relief throughout the medical research community. Dr. Donald Abrams observed that "you don't really appreciate what you're doing until something like this happens."<sup>83</sup> An AIDS researcher noted that had FIAU proved effective in combating HIV as originally hoped, the tragedy could have been far worse: "[m]any of us are . . . very, very grateful we're not talking about thousands of deaths."<sup>84</sup>

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<sup>78</sup> Thompson, *supra* note 1.

<sup>79</sup> Charles Marwick, *NIH Panel Report of "No Flaws" in FIAU Trial at Variance With FDA Report, New Probe Planned*, 272 JAMA 9 (1994).

<sup>80</sup> Schwartz, *supra* note 2.

<sup>81</sup> Thompson, *supra* note 1.

<sup>82</sup> *Id.*

<sup>83</sup> John Schwartz, *Researchers Seek Lessons from Drug Study Deaths*, WASH. POST, Sept. 28, 1993, at Z9.

<sup>84</sup> *Id.* (quoting Dr. Deborah Cotton, Harvard Medical School). The FDA's Dr. David Feigel, who is responsible for all antiviral drug licenses, calculated that had FIAU been an AIDS drug with expanded access, 500-1000 deaths would have occurred, rather than five. Garrett, *supra* note 8.

Among AIDS researchers, the sense of having dodged a bullet was magnified, for FIAU, like all four AIDS drugs that had been approved at that time (AZT, DDI, DDC, and D4T) is a nucleoside analogue.<sup>85</sup>

Rapidly, NIH, the FDA, Congress, and consumer groups expressed criticism of the trial. Public Citizen's Health Research Group (HRG) questioned the lack of preliminary Phase I studies of FIAU's effects on healthy subjects. When informed that no such studies were performed because FIAU was on an expedited approval track,<sup>86</sup> HRG seized the opportunity to argue against such regulations.<sup>87</sup> The FDA's Antiviral Drugs Advisory Committee concluded that the FIAU trial strongly demonstrated the need for rigorous, controlled Phase II testing of all drugs; one member observed "the pendulum swinging back" (away from rapid access to new therapies).<sup>88</sup> In late 1993, an FDA task force completed its report on the FIAU trials. The report made several criticisms concerning the adequacy of existing regulations, and set forth comprehensive recommendations on how to prevent future research calamities. These proposals later would form the core of the pending regulations amending the requirements for reporting adverse experiences that occur during clinical trials and post-marketing.<sup>89</sup>

Warning signs of FIAU's potential danger were visible well before the 1993 FIAU trial.<sup>90</sup> One death occurred in a 1989 test of a drug called FIAC, which turns into FIAU when introduced into the body; three participants in a 1990 trial died during a second course of treatment; and a fifth died following the 1992 trial. Although the FDA indicated that not all the deaths necessarily were attributable to FIAU, it is arguable that notice was available to the monitoring physicians.<sup>91</sup> Carlton Lee, who died on July 30, 1993, had almost dropped out of the 1992 trial due to excruciating neuropathy. A 1992 participant complained constantly to NIH physicians that his neuropathy was continuing long after he had ceased taking FIAU, and repeatedly made clear that he believed FIAU was to blame. The researchers knew, however, that the participant, a former alcoholic, had experienced neuropathy years earlier, to which they attributed his lingering discomfort.<sup>92</sup> In earlier trials, many patients (24 of 79) had experienced periods of grossly elevated levels of certain liver enzymes, test results that may have hinted at the results that followed. At the time, NIH doctors viewed these enzyme "flares" as the body's response to clearing the hepatitis B virus.<sup>93</sup>

The FIAU task force subsequently sent warning letters to Dr. Hoofnagle and other researchers alleging failure to conform with regulations for the protection of human

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<sup>85</sup> Schwartz, *supra* note 83 (pointing out, however, that nucleoside analogues show varying degrees of toxicity). See also *FIAU Experience Reaffirms Need for Well-Controlled Phase II Trials, Even for Life Threatening Diseases*, F-D-C REP. ("The Blue Sheet"), Sept. 29, 1993, at 9 (noting that DDI and AZT have been associated with rare occurrences of liver toxicities similar to those seen in FIAU trial subjects).

<sup>86</sup> See 21 C.F.R. § 312.80-.88; see also *supra* text accompanying notes 41-43.

<sup>87</sup> *FIAU Phase I Tests in Healthy Subjects Should Have Preceded Study of Patients With Hepatitis B*, F-D-C REP. ("The Blue Sheet"), Dec. 15, 1993, at 9.

<sup>88</sup> See *FIAU Experience Reaffirms Need*, *supra* note 85. Current FDA regulations state only that Phase II trials "are typically well controlled," i.e., it is not mandatory that they be so. 21 C.F.R. § 312.21(b) (emphasis added).

<sup>89</sup> John Schwartz, *Optimism May Have Led to Drug Tragedy*, WASH. POST, Nov. 16, 1993, at 6. See also *Adverse Experience Reporting Requirements*, 59 Fed. Reg. at 54,050.

<sup>90</sup> Schwartz, *supra* note 89 (quoting Commissioner Kessler that "in retrospect, the data were there, but they weren't put together").

<sup>91</sup> *Id.*

<sup>92</sup> Schwartz, *supra* note 2.

<sup>93</sup> *Drug Study Sponsors Should Submit "Worst-Case" Safety Data Analysis Semi-Annually*, F-D-C REP. ("The Pink Sheet"), Nov. 22, 1993, at 15.

subjects.<sup>94</sup> NIH conducted an evaluation of the trials in which it found no wrongdoing, and concluded that, from the vantage point of the NIH researchers, FIAU's toxicity was an unpredictable development. The NIH report specifically noted the difficulties in placing direct blame on FIAU for earlier subjects' deaths.<sup>95</sup> While the scope of the NIH study was narrower than the FDA report, the reports' respective conclusions are inconsistent on a fundamental level. To reconcile the disparate conclusions, Secretary of Health and Human Services Donna Shalala commissioned a study by the Institutes of Medicine (IOM).<sup>96</sup> The IOM report, which was not released until March 1995, essentially came to the same conclusions as the NIH study. Specifically, the reviewing committee found that in light of the unanticipated nature and timing of FIAU's toxicity, there was nothing to suggest that the tragedy was preventable, that the investigators had conducted the trials in a negligent fashion, or that the investigators were callous or insensitive to the needs and conditions of the patients whom they studied.<sup>97</sup>

Not surprisingly, for at least some of the FIAU subjects and their families, the ultimate allocation of responsibility for the tragedy will be determined in court. The first of these suits was brought against Eli Lilly alleging that FIAU was in a "defective condition," and that the drug company failed to warn of possible side effects.<sup>98</sup> At least five suits are pending or imminent; the consumer advocacy group Public Citizen has sued Eli Lilly and the FDA, seeking documents about FIAU, as well as information on deaths associated with other experimental drugs.<sup>99</sup> The NIH physicians possibly could be targets of legal action based on claims of medical malpractice and failure to provide informed consent. Several of the physicians were reprimanded for deficiencies in obtaining their subjects' informed consent.<sup>100</sup> The FDA informed consent regulations require merely that trial subject be informed of "reasonably foreseeable risks or discomforts."<sup>101</sup> The consent form the trial participants signed listed six potential risks, but contained only an oblique reference to the possible existence of unknown hazards: "FIAU is a new medication, and its side effects have not been completely described."<sup>102</sup> If a jury is persuaded that the NIH physicians had no reasonable basis to foresee that FIAU might worsen the hepatitis B or even cause death, the researchers will be deemed to have complied with the regulations' requirements. One medical ethicist objected to the term "new medication," and recommended that the form should have stated that the drug was "an experimental anti-viral compound."<sup>103</sup> In comparison, another prominent ethicist has stated that his "reading of the [FIAU] Clinical Research Protocol and the Informed Consent Form suggests that it adequately disclosed the risks of the study."<sup>104</sup>

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<sup>94</sup> *FIAU Investigators Receive FDA "Warning Letters,"* F-D-C REP. ("The Blue Sheet"), May 18, 1994, at 11 (finding deficiencies in protocol adherence, informed consent documents, recordkeeping, and Institutional Review Board reporting).

<sup>95</sup> Marwick, *supra* note 79.

<sup>96</sup> *Id.*

<sup>97</sup> *FDA Biannual Adverse Event Reporting Proposal Poses Impediment to Drug Development, IOM FIAU Report Says,* F-D-C REP. ("The Pink Sheet"), Mar. 20, 1995, at 22.

<sup>98</sup> Eva M. Rodriguez, *Drugmaker Defends Fatal Experiment,* LEGAL TIMES, Nov. 29, 1993, at 6.

<sup>99</sup> *Victims, Families Sue Over Deadly Liver Drug,* THE RECORD, Aug. 15, 1994 at 1 (Bergen Cty., NJ newspaper).

<sup>100</sup> See *FIAU Investigators Receive FDA "Warning Letters,"* *supra* note 94.

<sup>101</sup> 21 C.F.R. § 50.25(a)(2) (emphasis added).

<sup>102</sup> Altman, *supra* note 76. The enumerated risks included fatigue, nausea, skin rashes, suppression of the bone marrow, seizures, and [peripheral neuropathy]. *Id.*

<sup>103</sup> *Id.* (quoting Dr. Judith P. Swazey, Acadia Institute. Swazey further stated that "if the FIAU consent form was a 'model' [as claimed by Dr. Hoofnagle], there may be problems with other forms").

<sup>104</sup> Jay Katz, *Human Experimentation and Human Rights,* 38 ST. LOUIS U.L.J. 7, 10 n.12. Katz notes, however, that the form "did not make crystal clear that this was purely an experimental study," and that the

A failure to identify any experimental treatments, if not rectified elsewhere in the consent form, would constitute a violation of the informed consent regulations.<sup>105</sup> In any event, the complexity of the underlying medical and informed consent issues and the multiplicity of parties make it impossible to predict the outcome of any of these legal actions.

## V. THE FDA'S NEWLY PROPOSED RULES

The proposed amendments to the adverse experience reporting requirements would implement several key changes in the structure of drug trials, and impose significant post-market burdens on pharmaceuticals investigators.<sup>106</sup> The proposed regulations were published on October 27, 1994, for a ninety-day public comment period.<sup>107</sup> A central goal of the new rules is uniformity in the reporting process, and to that end the FDA has proposed a model form for reporting adverse events and product problems, set a uniform standard of semi-annual, post-market adverse experience reports, and claimed to simplify and facilitate the reporting and collection of data concerning adverse events.<sup>108</sup> The rules' most controversial elements would

amend the requirements for clinical study design and conduct and the sponsor reporting requirements in the [IND] regulations. These amendments are intended to provide more complete and accurate information that would enable sponsors, investigators, and FDA to determine serious toxicities of investigational drugs more expeditiously during clinical studies.<sup>109</sup>

These amendments, which are "largely the result of the recommendations of the FIAU task force,"<sup>110</sup> have come under harsh criticism from several directions. Epidemiologists and research statisticians contend that the additional clinical study design requirements are scientifically indefensible, and would muddle rather than clarify toxicity data.<sup>111</sup> Research physicians object strongly to the regulations which mandate the presumption that adverse events are the result of drug toxicity.<sup>112</sup> Investigators and pharmaceuticals manufacturers oppose the added costs resulting from unnecessarily delayed studies, and the excessive paperwork associated with more frequent and more detailed reporting.<sup>113</sup> Individual academic researchers complain that the burdens of additional mandatory reporting disproportionately affect their research projects.<sup>114</sup> The

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possibility of grave danger "also should have been highlighted, as it was not, in the . . . form." *Id.*

<sup>105</sup> 21 C.F.R. § 50.25(a)(1).

<sup>106</sup> See generally *infra* notes 108-46.

<sup>107</sup> 59 Fed. Reg. 54,046.

<sup>108</sup> *Id.* at 54,046, 54,048.

<sup>109</sup> *Id.* at 54,046.

<sup>110</sup> *Id.*

<sup>111</sup> See, e.g., Stephen W. Lagakos, Harvard School of Public Health, Comments to Proposed Rules 1 (Jan. 15, 1995) ("the fact that adverse event rates can vary considerably across patient populations, coupled with the uncertainty with which the rates of many serious adverse events are known, make me conclude that this proposed requirement is misguided and scientifically flawed . . .") (all Comments on file with author).

<sup>112</sup> See, e.g., John Phair, M.D., Chair, NIH's National Institute of Allergy and Infectious Diseases (NIAID), AIDS Clinical Trials Group, Comments 2 (Jan. 5, 1995).

<sup>113</sup> See Curtis L. Meinert, Johns Hopkins Center for Clinical Trials, Comments 1 (Feb. 17, 1995) (calculating that for a recent clinical trial, the amendments would require reports generating 63 times as much paper as existing regulations, i.e., a stack of paper 765 feet high).

<sup>114</sup> See, e.g., Abbey S. Meyers & Jess G. Thoene, M.D., National Organization for Rare Disorders, Inc., Comments 1 (Nov. 14, 1994) (the rules will be a significant barrier to clinical research on rare diseases); see

combined force of the criticisms makes a persuasive case for extensive alteration or abandonment of many of the FDA's proposed changes.

As an initial step to ensure that more events which may reveal hidden risks in ongoing clinical studies are reported, the rules seek to expand the definition of "serious" to include any adverse event occurring at any dose that "prolongs inpatient hospitalization, or necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure."<sup>115</sup> The latter clause has been attacked for its vagueness<sup>116</sup> and for its over-inclusiveness; one drug company's comment pointed out that the wording could encompass even minor interventions such as the repair of a broken or infected tooth.<sup>117</sup>

The proposed amendments governing INDA design and protocols would impose substantial new requirements. Current regulations require that the study protocol submitted to the FDA provide a listing of the study's objectives, information concerning the investigators, criteria for patient selection, and the estimated number of subjects.<sup>118</sup> In addition, investigators must provide a description of the study design (and the kind of control groups, if any), details concerning dose administration and duration, a list of clinical observations and measurements to be made, and delineation of the steps to be taken to monitor the drug's effects on humans and to minimize risk.<sup>119</sup> Through the new rules, the FDA intends to have investigators devise study designs that will make it easier to detect drug toxicity that mimics the underlying disease, prospectively identify observations that will trigger safety action, and summarize safety data at regular intervals "with systematic considerations of the possibility that the adverse events are drug related."<sup>120</sup> It is the last of these general goals that has provoked the greatest criticism from the pharmaceutical manufacturing and medical research communities.

One section of the rules would require protocols to describe clinical or abnormal laboratory outcomes that must be reported immediately to the sponsor.<sup>121</sup> In particular, "[t]he identified events and abnormal laboratory values are to include those that focus attention on toxicity that may target the same organs and body systems as the underlying disease. . . ."<sup>122</sup> Such detailed discussion in the text of the proposed regulation illustrates the profound influence on the drafting process exerted by the FIAU trial, in which investigators attributed the subjects' initial deterioration and abnormal laboratory results to either the progression of the underlying hepatitis B or to the drug's success at clearing the virus.<sup>123</sup> Although several comments suggested the wording was too narrow (and thus might cause investigators to focus inordinately on toxicities that resemble the underlying disease and to neglect other potential dangers),<sup>124</sup> the section has

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also Stephen Nightingale, M.D., Physicians Association for AIDS Care, Comments 1 (Jan. 23, 1995) (warning against further concentration of drug development authority "in the hands of a few industrial giants").

<sup>115</sup> 59 Fed. Reg. at 54,046. The current definition of "serious" adverse event is one that is "fatal or life-threatening . . . permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose." 21 C.F.R. §§ 310.305(b)(4), 312.32(a), 314.80(a).

<sup>116</sup> See Michael Goldrich, Deputy Dir. for Management and Operations, NIAID, Comments 2 (Jan. 5, 1995).

<sup>117</sup> Bonnie J. Goldmann, M.D. & Wendy P. Stephenson, Merck Research Laboratories, Comments 3 (Jan. 25, 1995).

<sup>118</sup> See generally 21 C.F.R. § 312.23(a)(6)(iii)(a)-(g).

<sup>119</sup> *Id.*

<sup>120</sup> 59 Fed. Reg. at 54,050 (emphasis added).

<sup>121</sup> *Id.* (to be codified at 21 C.F.R. § 312.23(a)(6)(iii)(h)).

<sup>122</sup> *Id.* at 54,057.

<sup>123</sup> See *supra* notes 90-93 and accompanying text.

<sup>124</sup> See Ronald J. Ziance, Sandoz Pharmaceuticals Corp., Comments 3 (Jan. 24, 1995).

some support among those submitting comments.<sup>125</sup> In a further effort to make the presence of drug-related toxicities more visible, the FDA proposed that sponsors “should consider” using a formal control group (either placebo or active) in studies that focus on safety when the underlying disease is likely to produce adverse events that may be confused with toxicity.<sup>126</sup> Although it may be unethical in certain circumstances to utilize placebo control groups where the underlying disease is life-threatening,<sup>127</sup> the section does not mandate the use of any control group (which nonetheless are utilized in many clinical trials<sup>128</sup>), and thus does not impose a significant burden on investigators. Unfortunately, this section is one of only a small number in the proposed regulations where the FDA has left open some flexibility in clinical trial design.

The following proposed section has been almost unanimously criticized in the public comments:

The sponsor shall estimate the expected incidence of deaths and serious adverse experiences in the study population that may arise from the underlying disease or from medications used to treat the underlying disease. Deaths or serious adverse experiences that exceed those estimates would create a presumption that the events are associated with the use of the investigational drug.<sup>129</sup>

Criticisms of this requirement have centered on the methodological impossibility and excessive costs of attempting to predict such incidences with any degree of accuracy.<sup>130</sup> Several organizations have pointed out the risk of error inherent in ascribing significance to adverse events that exceed thresholds, which are themselves somewhat arbitrary.<sup>131</sup> The dilemma facing sponsors and investigators is obvious: knowing that the occurrence of adverse events exceeding the threshold level would mandate submitting a safety report under the new regulations,<sup>132</sup> the incentive is to inflate the estimated frequency of underlying adverse events with resulting harm to the scientific integrity of the study. Such a broad requirement weakens the authority of the investigating physicians, who are arguably in the best position to judge whether adverse events are attributable to drug toxicity. Although the FIAU trial illustrates the potential danger in allowing investigators to retain such control, it is unwise to compel such a broad change in the focus of all clinical trials because of one study, even one gone so horribly wrong as the FIAU investigation.

A proposed section regarding the design of follow-up procedures further reveals

<sup>125</sup> See, e.g., Phair, *supra* note 112, at 1.

<sup>126</sup> 59 Fed. Reg. at 54,051 (to be codified at 21 C.F.R. § 312.23(a)(6)(iii) (i)). Compare *FIAU Phase I Tests in Healthy Subjects*, *supra* note 87 and accompanying text.

<sup>127</sup> See Samuel Broder, M.D., Director, National Cancer Institutes, NIH, Comments 1 (Jan. 9, 1995) (“Of special concern . . . is the issue of control populations in the design of Phase I *therapeutic* trials in both cancer and AIDS.”) (emphasis added). See also Rothman & Michels, *supra* note 66.

<sup>128</sup> See, e.g., John Siegfried, M.D., Pharmaceutical Research and Mfrs. of Am., Comments 5 (Jan. 25, 1995).

<sup>129</sup> 59 Fed. Reg. at 54,051 (to be codified at 21 C.F.R. § 312.23(a)(6)(iii)(j)).

<sup>130</sup> See, e.g., Goldrich, *supra* note 116, at 3 (“[G]iven the complexity of HIV . . . and its . . . medical management, we do not believe it is possible to construct a . . . valid background profile of anticipated event frequencies.”); see also Siegfried, *supra* note 128, at 5 (“Estimation of adverse events . . . is fraught with the likelihood of significant error.”).

<sup>131</sup> See, e.g., Stots B. Reece, M.D. & Lorraine M. Anderson, Hoffmann-LaRoche Inc., Comments 3 (Jan. 19, 1995) (“Such imprecise predictions could lead to inaccurate estimates of such events, and could result in misleading conclusions as to the drug’s toxicity.”); Lagakos, *supra* note 111, at 2.

<sup>132</sup> 59 Fed. Reg. at 54,048 (to be codified at 21 C.F.R. § 312.32(c)(1)(i)).

the influence of the FIAU trial in the drafting of the new regulations. The FDA sought to require that sponsors determine the duration and nature of the "appropriate" follow-up to clinical trials "based on preclinical data, experience with other members of the drug class, the drug's mechanism of action, and other human experience."<sup>133</sup> These factors echo concerns retrospectively observed in the FIAU experiment, in which an earlier trial of a related drug resulted in a patient's death.<sup>134</sup> Although some comments have expressed apprehension about long follow-up periods,<sup>135</sup> the proposed section's lack of strict standards for such periods is welcome, suggesting a flexibility in follow-up review that will allow sponsors to tailor trial designs according to the known characteristics of the experimental drug.

The FDA proposed more burdensome requirements for summary reports of ongoing clinical trials. Under existing regulations, sponsors must submit annual reports that include a summary of reported adverse events, the general progress of the trial, foreign market developments (i.e., disapprovals or license revocations), and protocol or manufacturing changes.<sup>136</sup> The proposed regulations would mandate such reports on a semi-annual basis, impose rigid new parameters within which to analyze the summary data, and grant the FDA power to place a trial on clinical hold for failure to submit such reports.<sup>137</sup> Noting that NIH investigators did not have an adequate overview of earlier FIAU trials, the FDA sought to compel sponsors to prepare cumulative analyses of all serious adverse events (and any adverse events resulting in study discontinuations) "*whether or not there is thought to be a possibility [that the event] was caused by a drug.*"<sup>138</sup> The proposed amendment further requires the sponsor's analysis to

*assume[] that the . . . drug is responsible for the [events], and refute, as feasible, this presumption with appropriate data and evaluations. The expected incidence of deaths and serious adverse experiences in the study population that may arise from the underlying disease or from medications used to treat the underlying disease that was estimated in the protocol should be considered in this evaluation.*<sup>139</sup>

The semi-annual reporting requirements, which are related to and dependent on the proposed section requiring estimates of underlying disease rates,<sup>140</sup> likewise have earned criticism during the public comment period. Clearly, establishing such a presumption is problematic in cases where the underlying disease process (e.g., AIDS) is so devastating that serious adverse events are often the rule rather than the exception,<sup>141</sup> thus making it more difficult to determine which adverse events actually were caused by the

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<sup>133</sup> *Id.* at 54,057 (to be codified at 21 C.F.R. § 312.23(a)(6)(iii)(k)).

<sup>134</sup> See *supra* note 91 and accompanying text.

<sup>135</sup> See, e.g., John N. Beidler, Johnson & Johnson, Comments 4 (Jan. 24, 1995) (noting that lengthy follow-ups are costly, and gradually lose scientific validity as subjects' medications, treatments, and disease states diverge over time).

<sup>136</sup> 21 C.F.R. § 312.32(a).

<sup>137</sup> 59 Fed. Reg. at 54,058-59 (to be codified at 21 C.F.R. § 312.33(b)).

<sup>138</sup> *Id.* at 54,058 (emphasis added). See also Schwartz, *supra* note 89 ("Kessler said the message of the new system will be, '[d]on't presume that there are other reasons for what is happening' when patients get sick.").

<sup>139</sup> 59 Fed. Reg. at 54,059 (to be codified at 21 C.F.R. § 312.33(b)(1)) (emphasis added).

<sup>140</sup> See *supra* notes 129-31 and accompanying text.

<sup>141</sup> See Phair, *supra* note 112, at 2 ("It should be obvious that all adverse events are not automatically the result of exposure to an investigational agent in studies of patients with . . . advanced HIV-1 infection or cancer.").

investigational drug. This presumption could lead to hasty terminations of experiments, compelled by the regulation's excessively cautious outlook.<sup>142</sup> While it could be argued that caution is never "excessive" where it saves lives, the proposed rules still are based on the flawed assumption that it is possible to meaningfully estimate the likelihood of adverse events in the underlying disease process.<sup>143</sup> In addition, while the "worst-case" presumption alone would require reporting a much greater number of events, the shift from annual to semi-annual reporting creates an immediate, significant increase in reporting burdens that may well not be medically justifiable.<sup>144</sup>

In addition to the proposed INDA amendments, the FDA sought to alter reporting requirements for adverse experiences associated with drugs already approved for interstate shipment. Current regulations require manufacturers to submit quarterly reports for the first three years following a drug's approval, and annual reports thereafter.<sup>145</sup> The FDA proposed establishing a uniform biannual requirement for periodic adverse experience reports.<sup>146</sup> Pharmaceutical manufacturers questioned whether the increased frequency will provide meaningful safety data for drugs that have been on the market for three years,<sup>147</sup> and several have advocated eliminating outright the annual reports for drugs that have been approved for five to seven years.<sup>148</sup>

It is difficult to avoid concluding that the proposed rules are a flawed attempt to uniformly apply the lessons from the FIAU case to all clinical trials. Indeed, the FDA's decision to incorporate the FIAU task force's recommendations so completely in drafting its proposed regulations is puzzling in light of the task force's statement that "it is impossible to know, in retrospect, whether an overview . . . [of the kind now proposed] . . . might have permitted detection of a pattern of cumulative . . . adverse events and thus predicted similar events."<sup>149</sup> In addition, one drug company questioned the appropriateness of basing such extensive changes on the task force's findings, in light of the fact that at the time the proposed rules were promulgated, the IOM review of the FIAU incident was pending.<sup>150</sup> In particular, now that the IOM report finally has issued and has largely refuted many of the assertions of the FDA task force that underlie the proposed regulations, it is apparent that the primary justifications supporting the proposed regulations have been weakened and debunked. Indeed, in the course of its report, the IOM took the opportunity to comment that the proposed requirement of cumulative semi-annual reports "will prove to be a substantial impediment to development of drugs to combat life-threatening diseases," and observed that "the timing of the promulgation is unfortunate."<sup>151</sup>

A further indication that the proposed rules go too far too hastily in mandating the reporting procedures is the chilled fashion in which TAG, the on-going advocate of

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<sup>142</sup> See Goldrich, *supra* note 116, at 5 ("if all events in an advanced HIV disease trial were attributed to the [drug] . . . an analysis would almost certainly reach statistically significant (and likely unwarranted) levels of concern about the toxicity of the investigational agent").

<sup>143</sup> See generally *supra* notes 130-31 and accompanying text.

<sup>144</sup> See Siegfried, *supra* note 128, at 7 ("strongly" opposing semiannual reporting (except in certain unique circumstances) as overly burdensome without increasing clinical understanding).

<sup>145</sup> 21 C.F.R. § 314.80.

<sup>146</sup> 59 Fed. Reg. at 54,048 (to be codified at 21 C.F.R. § 314.80(c)(2)(i)).

<sup>147</sup> See, e.g., Beidler, *supra* note 135, at 4; Siegfried, *supra* note 128, at 9-10.

<sup>148</sup> See Reeley & Anderson, *supra* note 131, at 7.

<sup>149</sup> FDA Task Force Rep., Fialuridine: Hepatic and Pancreatic Toxicity (Nov. 12, 1993) (*quoted in* Siegfried, *supra* note 128, at 2).

<sup>150</sup> See Beidler, *supra* note 135, at 1. See also *supra* notes 95-96 and accompanying text.

<sup>151</sup> FDA Biannual Adverse Event Reporting Proposal Poses Impediment, *supra* note 97.

rigorous efficacy testing, has greeted them. TAG spokesman Spencer Cox expressed concern that the rules may slow AIDS research, with the reporting procedures making it "more arduous to conduct large tests."<sup>152</sup> One passage in the National Institute of Allergy and Infectious Diseases' comments states the essential risks posed by the rules. While conceding the need for continued focus on the safety of clinical subjects, the Institute reminds the FDA that:

[t]here is, however, a delicate balance between this desire for improvements in safety monitoring and the certainty that rare and tragic events will occur in human experimentation even under the most stringent safety regulations and procedures. It would obviously be counter-productive if marginal improvements substantially delayed, added prohibitive impediments, or significantly increased the costs of discovery and development of useful new treatments.<sup>153</sup>

Ultimately, the proposed regulations err on the side of imposing excessive burdens, without a corresponding promise of tangible safety improvements. From commercial and clinical standpoints, the burdens that would be imposed by the regulations substantially outweigh their benefits, and the FDA would be (and has been) well advised to fundamentally alter them, perhaps by making the proposed stricter requirements applicable only to those drugs thought likely to be toxic. (Whether the FDA chooses to make changes, however, may not be significant in light of political developments that could make the FDA's proposed amendments moot.)

## VI. RELEVANT LEGISLATIVE ACTION

The ongoing debate between AIDS activists, drug companies, and the FDA on the proper scope of government regulation of INDs undoubtedly has been influenced by the Republican Party's takeover of Congress. The House Republicans' campaign rhetoric and early legislative successes reflect a concerted move away from government regulation, and proposed reform legislation made it increasingly apparent that the FDA will be a specific target for regulatory curtailment. The Republican campaign document and early legislative blueprint the "Contract With America" promises "the end of government that is too big, too intrusive, and too easy with the public's money."<sup>154</sup> The Contract is ostensibly "rooted in the core principles of Accountability, Responsibility, and Opportunity,"<sup>155</sup> and proclaims that "unelected bureaucrats have become . . . unresponsive to the public they are supposed to serve." It complains earnestly of both the usurpation of personal responsibility and "burdensome governmental regulations."<sup>156</sup>

Two particular legislative elements of the Contract that would significantly curtail FDA regulatory authority were approved in the House of Representatives.<sup>157</sup> The Job Creation and Wage Enhancement Act of 1995 passed in the House on March 3, 1995, and was referred to Senate committee.<sup>158</sup> The bill's sponsors claimed that it would de-

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<sup>152</sup> Quoted in Thomas J. Maier, *Death Changes the Rx.*, NEWSDAY, Oct. 29, 1994, at 21. TAG eventually declined to submit comments to the proposed rules due to a claimed lack of expertise in the statistical analysis of reporting requirements. Telephone conversation with Spencer Cox (Jan. 20, 1995).

<sup>153</sup> Goldrich, *supra* note 116, at 1.

<sup>154</sup> *Republican Contract With America* (Sept. 28, 1994) (available in LEXIS, Extra Library).

<sup>155</sup> *Id.*

<sup>156</sup> *Id.*

<sup>157</sup> See *infra* notes 158-64 and accompanying text.

<sup>158</sup> H.R. 9, 104th Cong., 1st Sess. (1995).

centralize and reduce the power of the federal bureaucracy, and increase the accountability of federal officials.<sup>159</sup> Toward that end, the bill would have required federal agencies to look closely at alternatives to proposed rules, prepare rigorous peer-reviewed risk assessments and cost-benefit analyses for any proposed or promulgated rules, and certify that no regulatory alternative would achieve an equivalent risk reduction when issuing final rules.<sup>160</sup> The proposed adverse experience reporting regulations' excessive cost to industry<sup>161</sup> and minimal safety benefits<sup>162</sup> cast doubt on the regulations' viability under a regime of cost-benefit analysis.

On February 24, 1995, the House passed The Regulatory Transition Act of 1995 (HRTA), which would have prohibited (or suspended) agency rulemaking actions from November 20, 1994, until December 31, 1995.<sup>163</sup> The HRTA's exceptions for agency actions that lessen regulatory burdens or which are "necessary because of an imminent threat to health or safety,"<sup>164</sup> would not have exempted the FDA's proposed regulations, which increase regulatory burdens, and could not be deemed necessary to combat "imminent" threats to health or safety.

On March 29, 1995, the Senate unanimously passed a revised version of the Regulatory Transition Act (SRTA), and requested the House's concurrence.<sup>165</sup> The SRTA imposed a moratorium on burdensome regulations through June 30, 1995, in order to provide Congress with an opportunity to review the proposed regulation, with power to issue a joint disapproval of the rule.<sup>166</sup> Before a final rule could take effect, the SRTA required agencies to submit to Congress copies of all rules, as well as detailed analyses thereof, at Congress's request.<sup>167</sup> The applicability of the SRTA to the adverse experience regulations was not certain, but was quite probable. The SRTA applied to "significant" rules, which was defined as any rule which the Office of Management and Budget (OMB) found "has an annual effect on the economy of \$100,000,000 or more, or adversely affects in a material way . . . a sector of the economy, productivity, competition . . . public health or safety."<sup>168</sup> OMB could have found that even the FDA's low estimates of the increased economic burden on industry<sup>169</sup> constituted a "material" adverse effect on the pharmaceutical industry and, as such, the regulations would have been subject to congressional review (and possible disapproval) under the SRTA.

Ultimately the Contract with America's specific regulatory reform provisions were not enacted through legislation. Rather, they became bogged down in disputes between the House and Senate, as "moderate Republicans and Democrats thought the legislation went too far and would hamstring agencies' attempts to model new rules."<sup>170</sup> The fail-

<sup>159</sup> *Id.*

<sup>160</sup> *Id.* § 421.

<sup>161</sup> *See, e.g.,* Siegfried, *supra* note 128, at 3 ("FDA's . . . estimate of total annual reporting cost . . . (\$24,030,100) is grossly understated. . . . The costs . . . will, in all likelihood, be a multiple of that. . . .").

<sup>162</sup> *See generally supra* notes 111, 130-32, 141-42. *See also* Meinert, *supra* note 113 (noting that it is possible the proposed changes could increase risks to trial subjects).

<sup>163</sup> H.R. 450, 104th Cong., 1st Sess. (1995).

<sup>164</sup> *Id.* ("imminent threats" are those which are "reasonably expected to cause death, serious illness, or severe injury . . . during the moratorium period") (emphasis added).

<sup>165</sup> 141 CONG. REC. H 3979 (Mar. 30, 1995) (message from the Senate).

<sup>166</sup> S. 219, 104th Cong., 1st Sess. (1995).

<sup>167</sup> *Id.* § 103.

<sup>168</sup> *Id.* § 106(2)(A)(I).

<sup>169</sup> 59 Fed. Reg. at 54,055 (estimating regulations' total cost to be \$24,030,100). *But see* Siegfried, *supra* notes 128, 160 (estimating costs to be a "multiple" of the FDA's figure).

<sup>170</sup> Cindy Skrzycki, *Slowing the Flow of Federal Rules: New Conservative Climate Chills Agencies' Activism*, WASH. POST, Feb. 18, 1996, at A1.

ure of Congress to pass laws overhauling the nation's regulatory structures does not mean, however, that the spirit of reform that motivated the bills has subsided.

The level of political activity specifically targeting the FDA has increased. Even before the 1994 elections there were hints of such a trend, as Speaker of the House Newt Gingrich labeled FDA Commissioner Kessler "a bully and a thug" for threatening to push for FDA regulation of tobacco.<sup>171</sup> Those favoring a less-intrusive role for the FDA are facing congressional oversight committees which, instead of pressuring the FDA to pursue enforcement, "are more likely to be hauling agencies [before them] asking them to explain why they're over-regulating or hassling a regulated industry."<sup>172</sup> An increasingly cohesive group of laissez-faire-minded think tanks, pharmaceuticals industry representatives, and congressional leaders now are working toward "a major restructuring" of the FDA.<sup>173</sup> The Cato Institute has dubbed the FDA "an example of gross interference with the free market."<sup>174</sup>

In specific proposals, some of the groups' representatives have spoken of eventual abolition or privatization of the FDA's functions, coupled with short-term incremental reforms.<sup>175</sup> At the first oversight hearing focusing on FDA medical device approval policies, Thomas Bliley Jr. (R-Va.), Chairman of the House Commerce Committee, announced he was prepared "to subject both the [FDCA] and the FDA to comprehensive overhaul in this Congress."<sup>176</sup> FDA officials hope that a public defense of their policies and successes, combined with reforms recommended by President Clinton, will help to parry congressional attacks.<sup>177</sup> The FDA has emphasized the decrease in average review times for NDAs (from thirty months in 1992 to twenty months in 1994) since Congress granted it authority to charge applicants fees to finance NDA reviews.<sup>178</sup> President Clinton's proposals include facilitating manufacturing changes, eliminating the requirement that companies submit environmental assessments, and exempting low-risk medical devices from premarket review.<sup>179</sup> While the FDA has made progress in speeding certain populations' access to drugs<sup>180</sup> and drug review in general,<sup>181</sup> industry advocates have attributed recent reductions in approval times to "a year-end spree designed to boost approval numbers."<sup>182</sup> Similarly, Peter Barton Hutt, former FDA Chief

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<sup>171</sup> Stan Crock et al., *A GOP Jihad Against Red Tape*, BUS. WEEK, Nov. 28, 1994, at 48 (quoting *Dateline* NBC television broadcast (Nov. 15, 1994)).

<sup>172</sup> Peter Stone, *Back Off!*, NAT'L J., Dec. 3, 1994, available in LEXIS, News library (quoting a lobbyist). See also Carol Byrne, *For Jubilant Republicans, a Down-Home Tale May Hold a Lesson*, STAR TRIBUNE (Minneapolis), Nov. 20, 1994, at 1 (Rep. Jim Ramstad's (R-Minn.) "pet cause" of getting the FDA to "clean up its act" has gone "from far right field to home plate.").

<sup>173</sup> Peter Stone, *Ganging Up On the FDA*, NAT'L J., Feb. 18, 1995, available in LEXIS, News library. The article details the efforts of Citizens for a Sound Economy, the Washington Legal Foundation, and the Gingrich-affiliated Progress and Freedom Foundation to broadcast incendiary advertisements, lobby Congress, and obtain contributions from drug companies in the fight against drug approval delays. The Washington Legal Foundation's print advertisements feature pictures of coffins, and call the FDA "a killer." *Id.*

<sup>174</sup> Saul Friedman, *Republicans Targeting FDA*, NEWSDAY, Feb. 27, 1995, at 4 (quoting Robert Moffit).

<sup>175</sup> *Id.*

<sup>176</sup> *FDA Panel Begins Oversight Hearings With Panel of Patients, Physicians*, HEALTH CARE DAILY, Mar. 31, 1995, available in LEXIS, News library.

<sup>177</sup> Benjamin Wittes, *Has FDA Gotten Its Act Together?*, LEGAL TIMES, Mar. 20, 1995, at 5.

<sup>178</sup> *Id.*

<sup>179</sup> *Clinton Offers Regulatory Reforms to Speed Approvals of Drugs, Devices*, MGMT. BRIEFING, Mar. 17, 1995, available in LEXIS, News library.

<sup>180</sup> See generally *supra* pt. III.

<sup>181</sup> See *supra* note 178 and accompanying text.

<sup>182</sup> Wittes, *supra* note 177 (quoting Samuel Kazman, General Counsel for the Competitive Enterprise Institute).

Counsel, doubts the FDA's willingness to self-reform, and advocates "brutally intrusive" legislation instead.<sup>183</sup>

Several recent developments suggest that "brutally intrusive regulation" will not be necessary, however, to implement significant changes in the FDA's workings. The last several months have seen the rapid approval of three new drugs to combat the AIDS virus. In March 1996, the FDA, "under intense Congressional pressure to hasten drug approvals,"<sup>184</sup> approved indinavir, the third protease inhibitor, a mere forty-two days after the submission of the new drug application.<sup>185</sup> The rapid approval of indinavir eclipsed a record that had been established earlier that month, when ritonavir was approved in seventy-two days after final application.<sup>186</sup> To further illustrate the shift at the FDA, Sidney Wolfe, Executive Director of Public Citizen's Health Research Group, has stated that "since the 1994 election, [the] FDA has all but ignored the petitions he has sent in requesting that the agency require drug manufacturers to warn patients about adverse health effects [of] certain drugs."<sup>187</sup> Wolfe's comments and the rapid drug approvals hint that the spirit of deregulation has begun to take firm root in the FDA, despite Congress's failure to pass a regulatory reform package.

## VII. CONCLUSION

In the current climate of anti-regulatory fervor and hastened drug approvals, however, there still can be heard the occasional plea to remember the FDA's traditional role as consumer protector. A Democratic congressman condemned "extreme positions . . . that give short shrift to patient needs," and noted that many of the more radical proposals to reform the FDA "are going to be opposed by industry."<sup>188</sup> Indeed, a national business publication recently warned against removing the efficacy requirement for new drugs, stating that "lowering the standard for approval would hurt both patients and industry. . . . [W]ithout FDA assurance that a new drug . . . work[s], companies will lose a key selling point for important new products."<sup>189</sup> The cautions voiced by the TAG and the AIDS research community are gaining credence as well, no longer drowned out by the sloganeering of ACT-UP. Yet the combined forces of industry, political reformers, and advocates of broad, early access to drugs have been steadily gaining the upper hand since the *Rutherford* decision. In this context, the proposed adverse experience reporting regulations only can be described as an exceptional development, one that may never truly succeed in influencing policy, because the regulations will likely be diluted by the FDA.

Representative Ron Wyden, who condemned the rush to denigrate the FDA,<sup>190</sup> nevertheless has indicated that he would support reforms leading to "faster approvals for breakthrough drugs."<sup>191</sup> Such reforms presumably would seek to reduce or eliminate costly, unnecessary regulatory hurdles such as those embodied in the proposed adverse

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<sup>183</sup> *FDA Unlikely to Self-Reform*, HEALTH CARE DAILY, Mar. 13, 1995, available in LEXIS, News library.

<sup>184</sup> Philip J. Hilts, *With Record Speed, F.D.A. Approves a New AIDS Drug*, N.Y. TIMES, Mar. 15, 1996, at A14.

<sup>185</sup> *Id.*

<sup>186</sup> *Id.*

<sup>187</sup> Skrzycki, *supra* note 170, at A1

<sup>188</sup> See Stone, *supra* note 173 (quoting Rep. Ron Wyden (D-Ore.)).

<sup>189</sup> *Reality Check*, BUS. WEEK., Dec. 12, 1994, at 6.

<sup>190</sup> See *supra* text accompanying note 188.

<sup>191</sup> See Stone, *supra* note 173.

experience reporting requirements. Of course, the danger of any such reform proposal is that the next "breakthrough" drug may turn out to be the next fialuridine, or worse. Such is the nature of medical experimentation, the risks of which can be reduced but never completely eliminated, not even by implementing the most rigid investigational criteria. It is the nature of severe, life-threatening illnesses that persons afflicted by them are far less likely to be deterred by the inherent risks of medical experiments than their healthy counterparts. In recent years, the FDA has made appropriate changes in some of its policies to accommodate this reality, and the public and special interest communities have come to take such streamlining procedures for granted, while clamoring for further reduction of hurdles to drug approval. In short, it appears that accelerated approval and treatment INDs (and the set of viewpoints of personal autonomy that inspired them) will remain in ascendance for at least the foreseeable future. As long as those rules' protective provisions are adequately designed and enforced, the changes effectuated by them should not be subjected to constraints similar to those imposed by the adverse event reporting regulations.

Even if the proposed regulations are diluted or abolished, however, the lessons from the FIAU trial will almost certainly linger in the collective minds of researchers and regulators. There will be no need for an explicit regulatory prohibition against excessive optimism, for the tragedy itself constitutes a stark reminder of the potential dangers of even the most "routine" clinical experiments. By diligently complying with current regulatory requirements for INDs, and providing subjects with all known information that may be relevant to deciding whether to participate in the study, such tragedies likely will remain infrequent.

There is a broad spectrum of views on the proper nature of government regulation of drugs. This span of beliefs stretches from the paternalism of the *Rutherford* court, through the middle ground of urging earlier access to drugs (particularly for those with life-threatening illnesses) while maintaining essential safety protections, to the radical views of system overhaul advocated by ACT-UP and other political and business activists whose views have found a new audience in the 104th Congress. Of these basic schools of thought, the most desirable and comprehensive is the centrist position, which does not require the FDA to surrender its regulatory authority, but recognizes that there are powerful arguments from medical science, economic efficiency, and personal autonomy that can and should act to limit the agency's reach. In the case of the proposed amendments to the adverse experience reporting requirements, the criticisms from each of these fields argue persuasively for a fundamental re-examination of the FDA's well-intentioned, though ill-conceived, regulatory course.