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## The Real Thalidomide Baby: The Evolution of the FDA in the Shadow of Thalidomide, 1960-1997

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<b>Citation</b>	The Real Thalidomide Baby: The Evolution of the FDA in the Shadow of Thalidomide, 1960-1997 (1997 Third Year Paper)
<b>Accessed</b>	February 19, 2015 9:35:05 AM EST
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# **The Real Thalidomide Baby:**

**The Evolution Of The FDA In The Shadow of Thalidomide, 1960 - 1997**

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**Food and Drug Law, Winter 1997**

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## **Introduction**

It is no exaggeration to state that the story of thalidomide is the story of the modern FDA. Thalidomide became history's most infamous drug in the late 1950s and early 1960s when it caused serious birth defects in thousands of newborns. Congress, reacting to the tragedy, quickly passed amendments to the Food, Drug, and Cosmetic Act which dramatically toughened the FDA's approach to new drugs. But the pendulum has recently begun to swing the other way: aggravation with the FDA's time-consuming and expensive approval process for drugs like thalidomide has led to expedited approval procedures and calls for reform.

This paper is intended to document the over thirty-year relationship between the FDA and thalidomide and to describe in some detail the new uses for that drug. The paper's secondary goal is to demonstrate the power and versatility of food and drug law online research; every source cited herein, with the exception of the course materials, is available to anyone with access to Westlaw and the World Wide Web.<sup>1</sup>

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<sup>1</sup>In order to illustrate this dimension of the paper, I will provide online "addresses" as part of the citation form even where

## The Original Uses Of Thalidomide

Thalidomide, one of the most notorious drugs in the world, was first developed and sold in Europe in the 1950s as a tranquilizer.<sup>2</sup> A West German company<sup>3</sup> brought it to market, and it was eventually sold by fourteen companies in forty-six countries. Doctors in those countries prescribed it to pregnant women as a relief for morning sickness, not knowing of the drug's horrible effect on their offspring.<sup>4</sup> By 1961 or 1962, thalidomide's teratogenic<sup>5</sup> effect on gestating children was widely recognized:<sup>6</sup> mothers taking the drug gave birth to children with severe deformities,<sup>7</sup> including blindness, deafness, missing limbs, and flipper-like appendages.<sup>8</sup> The exact number of victims is unknown; one newspaper reported the total as 8,000 in 1985,<sup>9</sup> 12,000 in 1991,<sup>10</sup> and 8,000 again in 1993.<sup>11</sup> The exact number is not important, though; the horror and outrage sparked by this disaster is.

Thalidomide was never approved by the FDA for use in the United States, and therein lies one of the FDA's

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the Bluebook does not require them.

<sup>2</sup>Brett Lowell, Growing Interest in Thalidomide, GMHC Treatment Issues (visited Jan. 6, 1997) <<http://www.gmhc.org/aidslib/ti/ti95b.html>>.

<sup>3</sup>The company, Chemie Grunenthal G.M.B.H., held the original U.S. thalidomide patent, Patent No. 2,830,991. Application of Hartop, 311 F.2d 249, 265 n.5 (C.C.P.A. 1962) (dissenting opinion).

<sup>4</sup>Thalidomide, Scourge of 1950s, May Block AIDS Virus Growth, Chicago Tribune, Jul. 1, 1993, at 6 [hereinafter Scourge], available in WL chitrib database.

<sup>5</sup>"Teratogenic" translates roughly as "deformative," or, in the words of a less sensitive era, "monster-producing," S. Rep. No. 1744 (1962), reprinted in 1962 U.S.C.C.A.N. 2884, available in 1962 WL 4821 (views of Senators Estes Kefauver, John A. Carroll, Thomas J. Dodd, Philip A. Hart, and Edward V. Long) [hereinafter Senate Report].

<sup>6</sup>Hartop, 311 F.2d at 265 n.5 (dissenting opinion) ("It appears to be a matter of general knowledge [in 1962] that thalidomide, although effective as a sedative in human beings, resulted in deformed offspring born to women who had taken it during pregnancy.").

<sup>7</sup>The vast majority of these children were born in Britain, Germany, and Japan. See Scourge, supra note 4, at 6.

<sup>8</sup>Thalidomide Victim Learns To Cope With Handicaps, Chicago Tribune, Aug. 27, 1985, at 10, available in WL chitrib database.

<sup>9</sup>Id.

<sup>10</sup>Firms Seek To Use Banned Thalidomide, Chicago Tribune, Apr. 11, 1991, at 12 [hereinafter Banned], available in WL chitrib database.

<sup>11</sup>See Scourge, supra note 4, at 6.

greatest success stories. In November of 1960, Dr. Francis Kelsey, the FDA official charged with overseeing thalidomide's New Drug Application (NDA), was concerned that thalidomide might cause neuropathy, a nerve disease, in some users.<sup>12</sup> She decided that the thalidomide NDA was incomplete and refused to approve it.<sup>13</sup> This kept thalidomide tied up just long enough, since in 1961 the drug's effect on newborn children became known.<sup>14</sup> In 1962, President Kennedy presented Dr. Kelsey with a gold medal — the Distinguished Federal Civil Service Award — for her efforts.<sup>15</sup>

This resounding success established the FDA's fundamental orientation on issues involving new drugs: better extremely safe than sorry. Preventing "another thalidomide" became the FDA's number one priority; as the current FDA Commissioner, Dr. David Kessler, put it, "Back in the 1960s and 1970s, post-thalidomide, the agency's mission was to keep unsafe products off the market."<sup>16</sup> Perhaps due to the visibility of inappropriate drug approvals, as opposed to the traditional *invisibility* of inappropriate failures to approve new drugs,<sup>17</sup> some of the "protect the public at all costs" attitude has carried through to the present day, with defenders of the status quo "constantly" reminding potential reformers of the thalidomide tragedy.<sup>18</sup>

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<sup>12</sup>See Senate Report, *supra* note 5.

<sup>13</sup>*Id.*

<sup>14</sup>*Id.* There is, however, a dispute as to whether Dr. Kelsey suspected thalidomide's teratogenic effects. See Steven B. Harris, The Right Lesson To Learn From Thalidomide (1992) (visited Jan. 6, 1997) <<http://w3.aces.uiuc.edu/DLM/Liberty/Tales/Thalidomide.html>>.

<sup>15</sup>Peter van der Linden, The Medal From The President (Nov. 11, 1994) (visited Jan. 7, 1997) <[http://www.best.com/~debunk/medical/dr\\_kelsey\\_thalidomide.html](http://www.best.com/~debunk/medical/dr_kelsey_thalidomide.html)> (citing The Insight Team, The Sunday Times of London, The Story of Thalidomide (1979)). Dr. Kelsey still works at the FDA, where she is currently the Director of the Division of Scientific Investigations. Disease Associations: Thalidomide To Be Used For AIDS Related Disorders Treatment, *AIDS Weekly Plus*, Nov. 25, 1996 [hereinafter Associations], available in 1996 WL 11522693.

<sup>16</sup>AIDS Activism Improves Medicine, *The Washington Post*, Oct. 16, 1992, at 3 [hereinafter Activism], available in <<http://the-tech.mit.edu/V112/N49/aids.49w.html>>.

<sup>17</sup>See Mary J. Ruwart, Death By Regulation (visited Jan. 7, 1997) <<http://www.creative.net/~star/fda.htm>> ("Former FDA Commissioner Alexander Schmidt noted that '... rarely, if ever, has Congress held a hearing to look into the failure of FDA to approve a new entity; but it has held hundreds of hearings alleging that the FDA has done something wrong by approving a drug...'"); see also Harris, *supra* note 14 ("Even if the local doctor understands the FDA's role in preventing the patient from being properly treated, 'Stenosis of the Government' is not a medical diagnosis, and cannot be written on a death certificate.").

<sup>18</sup>142 Cong. Rec. S9550-02 (1996) (citing Barbara Mikulski and Nancy Kassebaum, The FDA Can Work Better, *The Washington Post*, Jul. 26, 1996 [hereinafter Work Better]), available in 1996 WL 438360.

Public outrage provided strong support for the FDA's new approach from the beginning. Books were written on the topic,<sup>19</sup> and the word "thalidomide" entered our lexicon as a harsh pejorative.<sup>20</sup> The drug even made a pop culture appearance in Billy Joel's 1989 hit "We Didn't Start the Fire."<sup>21</sup> Recent studies of new uses for thalidomide have suffered accordingly, due largely to "disbelief on the part of many people — including physicians — that in light of its catastrophic history, thalidomide would ever be offered to anyone for any purpose."<sup>22</sup>

### Thalidomide And The 1962 Amendments

The change in the FDA's attitude towards new drugs was not the only result of the thalidomide tragedy. Just as the elixir sulfanilamide poisonings of the 1930s prompted Congress to pass the Food, Drug, and Cosmetic Act [hereinafter the Act] in 1938,<sup>23</sup> the horrors of the thalidomide babies pushed Congress to enact the so-called "Kefauver Amendments"<sup>24</sup> to the Act in 1962.<sup>25</sup>

Senator Kefauver's motives were noble: he intended the 1962 Amendments to "strengthen and broaden existing laws in the drug field so as to bring about better, safer medicine and to establish a more effective system of enforcement of the drug laws."<sup>26</sup> His bill was a complex piece of legislation, but its most important

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<sup>19</sup>See Linden, *supra* note 15.

<sup>20</sup>See, e.g., Tim Richard, Thalidomide Comes To The School House (visited Jan. 7, 1997) <<http://oonline.com/~emoryd/timr/tim9.html>> ("You would think that our lawmakers would hesitate before exposing students' minds to potential educational thalidomide.").

<sup>21</sup>Billy Joel, *We Didn't Start The Fire* (Columbia 1989) ("[1958:] Lebanon, Charles de Gaulle, California baseball / Stark-weather homicide, Children of thalidomide.."), available in <<http://www.imsa.edu/~kubiak/lyrics/Start.Fire.html>>.

<sup>22</sup>William Strain, Thalidomide May Be Useful Against HIV, AIDS Project (Apr., 1996) (visited Jan. 7, 1997) <<http://www.apla.org/apla/9604/twatch.html>>.

<sup>23</sup>Food, Drug, and Cosmetic Act, ch. 675, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301 - 395 (1994)).

<sup>24</sup>The 1962 Drug Amendments, 76 Stat. 780 (1962).

<sup>25</sup>The Evolution of U.S. Drug Law, FDA (visited Jan. 6, 1997) <<http://fda.gov//fdac/special/newdrug/benlaw.html>> [hereinafter Evolution].

<sup>26</sup>See Senate Report, *supra* note 5.

provision — the one which would do the most to bring about “better, safer medicine” — was section nine, which authorized the FDA to deny an NDA if there was not “substantial evidence” the drug would have its claimed effect.<sup>27</sup> The original Food, Drug, and Cosmetic Act had only required that new drugs be safe,<sup>28</sup> but Senator Kefauver argued that “the marketing of a safe but ineffective drug may well be positively injurious to the public health” since “[w]hen an ineffective drug is prescribed, it is usually in the place of an older but effective drug.”<sup>29</sup>

As several commentators have noted, there is some irony in the fact that the thalidomide tragedy prompted Congress to require a showing of efficacy and not just safety before FDA could approve a new drug. Thalidomide itself was an effective drug; that is, its tranquilizing qualities were never questioned, and it was even favored over other sedatives since it didn’t produce the usual “hangover effects.”<sup>30</sup> The problem with thalidomide, of course, was it was *unsafe* for use by pregnant women, an issue which the original FD&C Act, in theory, adequately addressed.<sup>31</sup> In fact, the introduction of the Kefauver Amendments in Congress predated public knowledge of thalidomide’s dangerousness.<sup>32</sup>

One provision of the 1962 Amendments did directly address part of the existing law which could have — but turned out not to have — been a problem in the FDA’s consideration of thalidomide. The statute previously dictated that an NDA would automatically be approved in sixty days unless it was specifically disapproved

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<sup>27</sup>Id.; see also 21 U.S.C. § 505(d) (explaining “Grounds for refusing application”).

<sup>28</sup>See Senate Report, supra note 5.

<sup>29</sup>See Senate Report, supra note 5.

<sup>30</sup>Id.

<sup>31</sup>Bruce N. Kuhlik, The Origins Of The Generic Drug Scandal And Proposed Amendments To The Food, Drug, and Cosmetic Act, 45 Food, Drug, and Cosm. L.J. 385, 389 (1990), available in WL jlr database.

<sup>32</sup>See Harris, supra note 14.

or unless its effective date were postponed up to a maximum of 180 days.<sup>33</sup> Congress, citing the need “to give the physicians of the FDA adequate time to appraise the safety and effectiveness of drugs,”<sup>34</sup> in section 6 of the bill extended the first deadline to ninety days and abolished the second.<sup>35</sup> Current law provides that the Secretary of Health and Human Services has 180 days from the filing of an NDA application to approve the application, convince the applicant to voluntarily delay it, or give the applicant an opportunity for a hearing within the next four months, after which the Secretary’s decision is due within three months.<sup>36</sup> In practice, this provision gave the FDA tremendous leverage over drug manufacturers. A company which refused to cooperate and voluntarily delay its NDA might find that NDA denied, perhaps on the grounds that the company developed insufficient information to justify approval, or its other drugs delayed in the approval process. In the drug approval process, time really is money, and a small company whose “burn rate” is hovering around one-half million dollars per month cannot afford to make an enemy of its regulator.

### **Dissatisfaction With The FDA: The New Procedures**

Despite the public support behind the 1962 Amendments, criticism soon began to tear at the edifice of the Food, Drug, and Cosmetic Act. The critics attacked on three fronts. First, as best articulated by Professor Peltzman, the 1962 Amendments resulted in the so-called “drug lag.”<sup>37</sup> Professor Peltzman argued that the Amendments, as of 1973, effectively prevented the development of twenty-five new chemical compounds per

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<sup>33</sup>See Senate Report, supra note 5.

<sup>34</sup>Id.

<sup>35</sup>Id.

<sup>36</sup>21 U.S.C. § 355(c)(1) (1994).

<sup>37</sup>Peter Barton Hutt and Richard A. Merrill, Food and Drug Law 580-582 (1991) (quoting Hearings Before the Subcomm. on Monopoly of the Senate Small Business Comm., 93d Cong., 1<sup>st</sup> Sess. (1973) (testimony of Sam Peltzman)).

year and resulted in a slowing pace of drug development generally.<sup>38</sup> Unsurprisingly, mandating that the FDA give proposed new drugs another layer of review slowed their approval. Second, the efficacy requirement of Kefauver's Amendments resulted in increased drug prices. Higher approval hurdles approximately doubled the research and development costs a company could expect to incur, and the Amendments acted as a barrier to market entry, weakening competition and allowing prices to rise in the drug industry.<sup>39</sup> Third, the sick objected that whether or not to use a drug is a personal choice, one that ought not be denied them so long as a drug was safe: "Each person needs to decide for themselves, in consultation with their physician... which risks they are willing to take."<sup>40</sup>

These criticisms did not fall on a deaf ear at Congress or at the FDA, and new, expedited and expanded procedures were employed to remedy the perceived problems. The FDA established a formal classification system for NDA and Investigational New Drug, or IND, applications which categorized proposals based primarily on their therapeutic potential.<sup>41</sup> The guidelines also took other factors into account, such as whether the proposal concerned an orphan drug (see below).<sup>42</sup> Then, in 1987, the FDA established a new category, Type AA, for potential AIDS therapies; type AA drugs receive the FDA's highest priority in the drug review process.<sup>43</sup>

In 1983, Congress passed the Orphan Drug Act<sup>44</sup> to provide incentives for manufacturers to develop orphans - drugs for treating rare diseases.<sup>45</sup> The law permits manufacturers advantageous tax deductions and exclusive marketing rights for new orphan drugs.<sup>46</sup>

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<sup>38</sup>Id.

<sup>39</sup>Id.

<sup>40</sup>See Ruwart, supra note 17.

<sup>41</sup>Dixie Farley, Benefit Vs. Risk: How FDA Approves New Drugs, FDA (visited Jan. 22, 1997) <<http://www.fda.gov/fdac/special/newdrug/benefits.html>>.

<sup>42</sup>Drug Review Priorities, FDA (visited Jan. 22, 1997) <<http://www.fda.gov/fdac/special/newdrug/benrev.html>>.

<sup>43</sup>Expanded Access And Expedited Approval Of New Therapies Related To HIV/AIDS, FDA (visited Jan. 6, 1997) <<http://www.fda.gov/oashi/aids/expanded.html>> [hereinafter HIV/AIDS].

<sup>44</sup>Orphan Drug Act, 96 Stat. 2049 (1983).

<sup>45</sup>See Evolution, supra note 25.

<sup>46</sup>Id.



The FDA has also set up programs under its “compassionate use” framework to allow access to unapproved drugs on a case-by-case basis for patients whose serious illnesses have not responded to other therapies.<sup>47</sup> The FDA will invoke the primary compassionate use mechanism, the Treatment IND, if the requested drug is reasonably safe, if there are adequate protections of the patient such as informed consent, and if the doctor administering the drug keeps records as to its effect on the patient.<sup>48</sup> The FDA significantly expanded and revised the Treatment IND program in 1987.<sup>49</sup> A related mechanism, the “parallel track” policy, gives patients who are unable to participate in clinical studies access to untested drugs.<sup>50</sup>

The FDA has also instituted expedited review and accelerated approval for new drugs. Expedited review, begun in 1988, allows the FDA to assist manufacturers in setting up trials and to waive the phase III study.<sup>51</sup> Under accelerated approval, begun in 1992, the FDA may allow promising drugs to reach the market before their complete effectiveness is demonstrated.<sup>52</sup>

### **The New Uses Of Thalidomide Under Expanded And Accelerated FDA Procedures**

After thalidomide’s fall from grace, few people imagined that it would ever be prescribed again. The surprising truth, however, is that thalidomide has been in nearly constant use since scientists discovered

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<sup>47</sup>Ken Flieger, FDA Finds New Ways To Speed Treatments To Patients, FDA (1995) (visited Jan. 22, 1997) <<http://fda.gov/fdac/special/newdrug/speeding.html>>; John S. James, Thalidomide For Wasting Syndrome: Progress Toward Compromise, AIDS Treatment News (Nov. 3, 1995) (visited Jan. 7, 1997) <<http://www.thebody.com/atn/234.html#Thalidomide>>.

<sup>48</sup>Hearings Before the Senate Comm. on Labor and Human Resources, 104th Cong., 2d Sess. (Jul. 30, 1996) (testimony of Jerold Mande) [hereinafter Mande].

<sup>49</sup>See Flieger, supra note 47.

<sup>50</sup>Id.

<sup>51</sup>See Mande, supra note 48.

<sup>52</sup>Id.; see also Flieger, supra note 47.

its teratogenic effects over thirty years ago.<sup>53</sup> This began after an Israeli doctor, treating a patient with Hansen's disease, or leprosy, administered thalidomide in an attempt to sedate his patient.<sup>54</sup> The doctor found that not only did the medication calm the patient, it also helped to fight the disease.<sup>55</sup> Leprosy patients are the primary consumers of thalidomide today,<sup>56</sup> and the drug is available through the U.S. Public Health Service as part of a compassionate use protocol.<sup>57</sup> Celgene, one of the corporations investigating new uses for thalidomide, received Orphan Drug status for its use of thalidomide as a leprosy treatment in 1993<sup>58</sup> and is expected to submit an NDA for that indication in early 1997.<sup>59</sup>

Researchers, interested in thalidomide's unexplained success against leprosy, began to investigate the drug.<sup>60</sup> They knew that leprosy is the result of a bacterial infection and that some leprosy patients suffer from a skin condition known as erythema nodosum leprosum, or ENL, if the disease interferes with their immune system.<sup>61</sup> Studies indicated that thalidomide, a drug with no antimicrobial effects (i.e. thalidomide couldn't fight the leprosy bacteria itself) was very effective in treating ENL, so scientists reasoned that thalidomide acted directly on the immune system.<sup>62</sup> Further experiments showed that thalidomide reduced the immune system's production and release of a certain hormone-like protein — tumor necrosis factor, or TNF — which

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<sup>53</sup>Denny Smith, Thalidomide And HIV: Several Possible Uses (Apr. 21, 1995) (visited Jan. 6, 1997) <<http://library.jri.org/library/news/atn/atn221g.html>>.

<sup>54</sup>Wendy Maritz, Thalidomide - Hope For HIV And TB Sufferers, Strategic Health Review (Nov. 28, 1996) (visited Jan. 6, 1997) <<http://www.web-ads.co.za.html>>.

<sup>55</sup>Id.

<sup>56</sup>Carol Blaney, Second Thoughts About Thalidomide, Medical Sciences Bulletin (visited Jan. 6, 1997) <[http://pharminfo.com/cgi-bin/print\\_hit.../thalidomide.html](http://pharminfo.com/cgi-bin/print_hit.../thalidomide.html)>.

<sup>57</sup>See Banned, *supra* note 10.

<sup>58</sup>Thalidomide Now Approved By FDA For A Fourth Application, Doctor's Guide (Mar. 20, 1996) (visited Jan. 12, 1997) <<http://www.plsgroup.com/dg/6cfe.htm>> [hereinafter Fourth].

<sup>59</sup>FDA Application: Celgene Seeks O.K. To Use Thalidomide In Leprosy Cases, Chicago Tribune, Dec. 26, 1996, at 7 [hereinafter Application], available in WL chitrib database.

<sup>60</sup>See Blaney, *supra* note 56.

<sup>61</sup>See Lowell, *supra* note 2.

<sup>62</sup>Id.

acts as an intercellular messenger.<sup>63</sup> In normal concentrations TNF helps the body fight pathogens, but certain chronic conditions cause the body to overproduce it, leading to a number of unpleasant effects.<sup>64</sup> This was confirmed by one AIDS study in which researchers administered TNF itself to patients and found it significantly aggravated their symptoms.<sup>65</sup> Thalidomide's ability to inhibit the body's use of TNF, like other TNF inhibitors, thus generally doesn't attack the disease directly; instead it "attack[s] an underlying immune abnormality that occurs because of the disease... mak[ing] the disease easier to deal with in a more direct fashion."<sup>66</sup> In short, thalidomide prevents the immune system of a person suffering from a chronic illness like leprosy from actually harming the person.

Understanding the role of TNF in leprosy was not the most significant finding of the researchers whose work is described above. Leprosy is, after all, a rare,<sup>67</sup> though terrible, disease. Instead, the real insight was the role thalidomide might play against other chronic diseases in which the body's TNF overproduction causes serious and long-term harm: "Once the mechanism [of action] in leprosy was established, we looked at other diseases associated with high levels of TNF."<sup>68</sup> This second-stage research has involved a large number of afflictions. Diabetes research indicates that TNF may have an impact on a diabetic's insulin absorption and use, as well as on glucose uptake, and researchers at Andrulis,<sup>69</sup> another company researching new uses for thalidomide, have conducted a phase II trial of the drug.<sup>70</sup> Andrulis researchers are further investigating whether the devastating neurological damage associated with Alzheimer's disease can be mitigated

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<sup>63</sup>Id.

<sup>64</sup>Mark Bower, Thalidomide, Project Inform (last modified Jan. 20, 1996) <[www.projinf.org/fs/thalido.html](http://www.projinf.org/fs/thalido.html)>.

<sup>65</sup>See Lowell, supra note 2.

<sup>66</sup>See Blaney, supra note 56.

<sup>67</sup>Slightly over 2,000 new leprosy cases were reported in the United States between 1984 and 1993. See Application, supra note 59.

<sup>68</sup>Katie Rodgers, Thalidomide's Effect On AIDS And TB Under Scrutiny, Drug Topics, Mar. 7, 1994, at 24, available in 1994 WL 2885995.

<sup>69</sup>Andrulis' web site is located at <<http://www.andrulis.com>>.

<sup>70</sup>Katie Rodgers, Diabetes Care: New Research, New Hope, Drug Topics, Jun. 12, 1995, at 62, available in 1995 WL 8066442.

by thalidomide.<sup>71</sup> The company holds a patent for the use of thalidomide in the treatment of Alzheimers and other neurological disorders.<sup>72</sup> Celgene<sup>73</sup> is also investigating thalidomide's potential as a brain cancer therapy.<sup>74</sup> Still other researchers are looking at uses for thalidomide in the treatment of bacterial meningitis, rheumatoid arthritis, multiple sclerosis, tuberculosis, and a variety of other diseases.<sup>75</sup>

At least judging by the amount of attention it has garnered, however, the most exciting area of thalidomide research involves HIV and AIDS. While ordinarily characterized as an "immune deficiency," a term which seems to indicate that the body's immune system is incapable of reacting to disease, HIV also causes an "autoaggressive" reaction, leading to the overproduction of TNF.<sup>76</sup> As with other diseases, too much TNF aggravates the symptoms of AIDS, which include: prurigo nodularis, itchy bumps on the skin;<sup>77</sup> diarrhea;<sup>78</sup> ulcers;<sup>79</sup> and cachexia, a severe weight loss condition also known as "wasting."<sup>80</sup> Thalidomide currently is being tested as a therapy to all of those symptoms.

Most importantly, unlike thalidomide research for other diseases, AIDS-related research has also uncovered evidence that thalidomide may actually help retard the development of the disease itself. Experiments have

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<sup>71</sup>Thalidomide Studied For Multiple Sclerosis, Drug News & Perspectives, Nov. 28, 1995 [hereinafter MS], available in WL drugnews database.

<sup>72</sup>Andrulis Announces Collaboration, Patent Using Thalidomide For Alzheimer's, Drug News & Perspectives, Sep. 5, 1995, available in WL drugnews database.

<sup>73</sup>Celgene's web site is located at <<http://www.chem.com/celgene/>>.

<sup>74</sup>Thalidomide, EntreMed Clinical Data, R&D Focus Drug News, Dec. 9, 1996, available in 1996 WL 13640914.

<sup>75</sup>See, e.g., Rodgers, supra note 68; MS, supra note 71.

<sup>76</sup>See Smith, supra note 53.

<sup>77</sup>Prurigo Nodularis: Thalidomide (last modified Jan. 26, 1996) <<http://galen.library.ucsf.edu/aidsrials/trials/trial10124.html>>.

<sup>78</sup>Edward King, Thalidomide And AIDS (visited Jan. 6, 1997) <<http://www.dircon.co.uk/nam/atu/31part1.html>>; Thalidomide Now Available To Treat AIDS Weight Loss, Medical Tribune (Jun. 6, 1996) (visited Jan. 6, 1997) <<http://www.medscape.com/News/jobson/MedTrib/obgyn/1996/v03.n11/Thalidomide.html?>>.

<sup>79</sup>See King, supra note 78; Lowell, supra note 2. Andrulis plans to file an NDA for this indication in early 1997. See Associations, supra note 15.

<sup>80</sup>See Lowell, supra note 2; Thalidomide Submitted for NDAs For Use In Leprosy And AIDS Cachexia, Doctor's Guide (Nov. 11, 1996) (visited Jan. 12, 1997) <<http://www.pslgroup.com/dg/daa6.htm>>.

shown that TNF can both activate latent HIV viruses<sup>81</sup> and enhance HIV replication.<sup>82</sup> It is thus possible that a TNF inhibitor such as thalidomide may actually reduce a patient's "viral burden."<sup>83</sup>

Perhaps unsurprisingly, given the constant pressure applied by AIDS activists to the FDA,<sup>84</sup> AIDS-related indications of thalidomide have been the beneficiary of the full range of expedited and expanded FDA procedures. Celgene has received Orphan Drug status for thalidomide's use against both cachexia and mouth ulcers,<sup>85</sup> and Andrus won an Orphan Drug designation for thalidomide's use against a different type of mouth sore.<sup>86</sup> Treatment INDs and parallel tracking are available to sufferers of both ulcers and cachexia.<sup>87</sup> The FDA also has invoked its expedited review by assisting the corporations in designing and implementing clinical trials,<sup>88</sup> and by allowing phases II and III of the required studies to be combined.<sup>89</sup> The devotion of the FDA's time and resources seems to have paid off: Celgene plans to apply for an NDA for thalidomide's use against cachexia early this year.<sup>90</sup>

In the rush to test thalidomide as a treatment for all of those diseases and symptoms, the drug's most obvious lesson — the potential for devastating birth defects — has not been forgotten.<sup>91</sup> An FDA advisory committee held two days of hearings on this subject in November, 1996,<sup>92</sup> where experts advised that the

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<sup>81</sup>See Lowell, supra note 2.

<sup>82</sup>See Smith, supra note 53.

<sup>83</sup>See Lowell, supra note 2.

<sup>84</sup>See Activism, supra note 16.

<sup>85</sup>See Fourth, supra note 58.

<sup>86</sup>Treatment: Thalidomide Approved As Treatment For AIDS-Associated Ulcers, AIDS Weekly, Jun. 12, 1995 [hereinafter Ulcers], available in 1995 WL 2242284.

<sup>87</sup>Ivy Fleischer Kupec, Thalidomide Update, FDA (Feb. 26, 1996) (visited Jan. 6, 1997) <<http://fda.gov//bbs/topics/ANSWERS/ANS00714.html>>.

<sup>88</sup>Id.

<sup>89</sup>See Ulcers, supra note 86; Cachexia (Treatment): Pivotal Trial Completed For Thalidomide In AIDS Patients, AIDS Weekly Plus, Oct. 21, 1996, available in 1996 WL 11522467; Rodgers, supra note 68.

<sup>90</sup>Celgene To Ask FDA Approval For Thalidomide In AIDS Use, Nando (Jul. 9, 1996) (visited Jan. 7, 1997) <[http://www.nando.net/newsroom/ntn/health/070996/health7\\_9222.html](http://www.nando.net/newsroom/ntn/health/070996/health7_9222.html)>.

<sup>91</sup>At least not in this country; Brazil, however, already has another thalidomide generation. See Associations, supra note 15.

<sup>92</sup>Thalidomide Hearings, Drug Topics, Oct. 21, 1996, at 22, available in 1996 WL 11132593.

FDA consider mandating two forms of birth controls for every pre-menopausal non-sterile woman involved in any thalidomide study.<sup>93</sup> Some researchers, taking no chances, have completely barred pregnant or nursing women from participating in their studies.<sup>94</sup> This has not set well with some AIDS interest groups, who argue that “[p]eople facing serious health concerns deserve to make their own informed treatment decisions.”<sup>95</sup> Given the horror of the previous generation of thalidomide babies, however, they are unlikely to prevail.

## Current Events

The interrelationship between thalidomide and the evolution of the FDA did not stop at the FDA’s recent procedural innovations. Arguments still swirl around the controversial drug and the FDA’s handling of it and similar drugs. But the attacks of the FDA’s critics are not new; in fact, they are the same criticisms which led the FDA to implement its new procedures only a few years ago.

The alleged “drug lag” is again at the heart of the debate. Citing the now-familiar proposition that “[p]atients can be harmed by delay in approving safe and effective new medicines just as they can by the approval of unsafe new medicines,”<sup>96</sup> reformers have accused the FDA of adhering to its thalidomide-centered approach to drug approval.<sup>97</sup> One particularly harsh critic even maintains that the FDA’s glacial review of beta-blockers resulted in the death of hundreds of thousands by cardiac arrhythmia.<sup>98</sup> Critics also attack the drug review process as being too costly, averaging nearly \$350M per drug.<sup>99</sup> Finally, critics argue that a chronically and

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<sup>93</sup>See Associations, *supra* note 15.

<sup>94</sup>See Prurigo Nodularis: Thalidomide, *supra* note 77.

<sup>95</sup>See Smith, *supra* note 53.

<sup>96</sup>See Work Better, *supra* note 18.

<sup>97</sup>141 Cong. Rec. E1273-02 (1996) (quoting James P. Driscoll, The FDA Can Work Better, The Los Angeles Times, Jun. 15, 1996), available in 1996 WL 438360.

<sup>98</sup>See Harris, *supra* note 14.

<sup>99</sup>The Access to Medical Treatment Act: Hearings on S. 1035 Before the Senate Comm. on Labor and Human Resources, 104<sup>th</sup> Cong. (1996) (opening statement of Senator Kassebaum, Committee Chair) [hereinafter Kassebaum], available in 1996

terminally ill person's decision to take a drug should rest between that person and their doctor alone.<sup>100</sup> They reason that efficacy is irrelevant for a new drug with the potential of treating patients with diseases like AIDS, since with the drug sufferers might get better, but without the drug they will surely die; so why not let them make their own treatment decisions?

The FDA takes strong issue with these accusations. Dr. Kessler put it bluntly: "The FDA is a world-wide leader when it comes to reviewing and approving new drugs rapidly and efficiently," so "[i]t is time to put to rest the incorrect perception that American patients generally suffer from a so-called drug lag."<sup>101</sup> The FDA published a report in 1995, entitled "Timely Access to New Drugs in the 1990s: An International Comparison," which demonstrates that, on average, the FDA approves drugs at least as fast as, if not faster than, its counterparts in other countries.<sup>102</sup> The FDA also points out that AIDS-related pharmaceuticals are approved particularly quickly: of the eight antiretrovirals approved as of June 1996, the longest took six months.<sup>103</sup> Finally, the FDA notes that 1996 was its best year on record for drug approvals, as one hundred and thirty-one new drugs were approved, a sixty percent increase over 1995.<sup>104</sup> Dr. Kessler, speaking to the Food and Drug Law Institute, noted that the FDA approved forty-six New Molecular Entities (NMEs<sup>105</sup>) in fiscal year 1996, an approximate one-hundred percent increase over recent years.<sup>106</sup> As for why it should

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WL 10830240.

<sup>100</sup>141 Cong. Rec. E1424-01 (1995) (statement of Rep. Peter A. Defazio), available in 1996 WL 411624. This sentiment also underlies the dispute in Quill v. Vacco, one of the most important cases heard by the Supreme Court in 1997. See Interview: Dr. Timothy Quill Discusses Doctor-Assisted Suicide, CBS This Morning, Jan. 8, 1997, available in 1997 WL 5621064.

<sup>101</sup>Kessler Denies FDA's Time Lag In Reviewing And Approving New Drugs, Pharmaceutical Business News, Dec. 20, 1995, available in 1995 WL 9599578.

<sup>102</sup>See HIV/AIDS, supra note 43.

<sup>103</sup>Id.

<sup>104</sup>Donald C. McLearn, FDA Approvals In 1996 Set New Records, FDA (Jan. 14, 1997) (visited Jan. 22, 1997) <<http://www.fda.gov/bbs/topics/ANSWERS/ANS00781.html>>.

<sup>105</sup>NMEs are "products containing an active substance that had never before been approved for marketing in any form in the United States." Id. FDA considers them a particularly good symbol of its efficiency in getting new drugs to patients. David Kessler, Remarks to the Food and Drug Law Institute (1996), available in <<http://www.fda.gov/opacom/kessler.html>>.

<sup>106</sup>Id.

still review drugs for effectiveness even when patients suffer from fatal diseases, the FDA responds that the critically ill need to be protected from health care quacks and from substituting ineffective treatments for effective ones.<sup>107</sup>

The current debate over the drug approval process is complicated somewhat by the presence of the so-called “buyer’s clubs,” organizations of activists who break the law to make unapproved drugs available to the afflicted, often those with AIDS.<sup>108</sup> These groups, who feel it is “patronizing” for the FDA to tell AIDS-sufferers that they “can’t take control of their own therapy,”<sup>109</sup> have set up their own compassionate use programs, participation in which generally requires a doctor’s prescription and a patient’s informed consent.<sup>110</sup> The FDA repeatedly warned the clubs to stop supplying thalidomide,<sup>111</sup> but the clubs refused until a meeting between them, the FDA, and Celgene, in which they agreed to stop supplying the drug when the FDA made it widely available.<sup>112</sup>

Whatever advances the FDA’s expedited and expanded procedures represent, AIDS patients have continued to demand access to thalidomide.<sup>113</sup> Responding to such pressure, Congress has jumped into the fray with two pieces of proposed legislation: The Access to Medical Treatment Act [hereinafter the Access Act] and the Food and Drug Administration Performance and Accountability Act of 1995 [hereinafter the Performance Act].

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<sup>107</sup>See Mande, *supra* note 48.

<sup>108</sup>AIDS Patients Use Illicit Buyer’s Clubs To Get Test Drugs, *The Atlanta Journal and Constitution*, Nov. 4, 1991 [hereinafter *Illicit Clubs*], available in 1991 WL 7833153. A list of AIDS buyers clubs is available at <<http://immunet.org/atn/ZQX23808.html>>.

<sup>109</sup>See *Illicit Clubs*, *supra* note 108.

<sup>110</sup>FDA And Underground Thalidomide, GMHC Treatment Issues (visited Jan. 6, 1997) <<http://www.gmhc.org/aidslib/ti/ti95/ti95ba.html>>.

<sup>111</sup>See Lowell, *supra* note 2.

<sup>112</sup>See James, *supra* note 47.

<sup>113</sup>See *Associations*, *supra* note 15.



The Access Act,<sup>114</sup> sponsored by Senate Minority Leader Tom Daschle and cosponsored by at least sixteen other senators,<sup>115</sup> would allow patients access to an unapproved drug if there is no evidence that it is unsafe, if the manufacturer is licensed, and if informed consent is obtained.<sup>116</sup> Essentially, the Access Act amounts to a repeal of the efficacy provisions of the 1962 Amendments, at least so far as certain drugs and patients are concerned. Senator Daschle, testifying before the Senate Labor & Human Resources Committee, said that “People should have the right to choose from among a full range of medical treatment options — particularly people who suffer from chronic and potentially fatal conditions that do not respond to conventional treatments.”<sup>117</sup> Jerold Mande, Commissioner Kessler’s Executive Assistant, delivered the FDA’s response to the Committee.<sup>118</sup> Mande pointed to the FDA’s recent treatment of thalidomide as evidence of the FDA’s “flexibility and open mindedness” and explained the various ways in which the FDA is able to speed approval and access to promising new drugs.<sup>119</sup> Mande also repeated the FDA’s position on unapproved alternative therapies: allowing access to unapproved drugs exposes vulnerable patients to unscrupulous snake-oil salesmen and may encourage such patients to substitute ineffective therapies for efficacious ones.<sup>120</sup> Senator Kassebaum, the Committee Chair, stated the dilemma succinctly: “The fundamental question before us today is how to achieve [the] balance between freedom of choice, on the one hand, and a reasonable assurance of safety and effectiveness, on the other.”<sup>121</sup>

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<sup>114</sup>S. 1035, 104<sup>th</sup> Cong. (1995), [available in](#) WL cong-billtxt database; H.R. 2019, 104<sup>th</sup> Cong. (1995), [available in](#) WL cong-billtxt database.

<sup>115</sup>[Access to Medical Treatment Act](#), Natural Health Village (visited Jan. 12, 1997) <<http://199.170.0.141/townhall/federal/access2med.html>>.

<sup>116</sup>[Bill to Increase Alternative Medicine Access Has Many Supporters and Many in Doubt](#), Health Legislation & Regulation, Jul. 31, 1996, [available in](#) 1996 WL 11279285.

<sup>117</sup>[Medical Treatment: Hearings on S. 1035 Before the Senate Comm. on Labor and Human Resources](#), 104<sup>th</sup> Cong. (1996) (statement of Senator Daschle), [available in](#) 1996 WL 10830241.

<sup>118</sup>[See](#) Mande, [supra](#) note 48.

<sup>119</sup>[Id.](#)

<sup>120</sup>[Id.](#)

<sup>121</sup>[See](#) Kassebaum, [supra](#) note 99.

The Performance Act, sponsored by Senator Kassebaum, is an attempt to answer that question. Her bill would “substantially shorten and make more efficient new product development and FDA review times without compromising either safety or effectiveness.”<sup>122</sup> The Performance Act would establish agency performance standards, shorten new drug approval timetables, and require the FDA to assist companies by helping to design test trials and by telling them what standards will be used to evaluate new drugs.<sup>123</sup> In short, Senator Kassebaum wants the best of both worlds: fast and efficient yet full and complete drug review. Dr. Kessler, testifying on the bill, said that while he shared her goals, he did not believe that the FDA could meet the bill’s requirements without additional resources.<sup>124</sup> Senator Kennedy, speaking on the floor of the Senate, predicted that the Performance Act would place the FDA in the grips of industry, leading to crises similar to Britain’s mad-cow disease disaster.<sup>125</sup>

## Conclusion

The exact resolution of the debate between FDA review and patient autonomy is, at this stage, unclear. Regardless, it appears certain that thalidomide’s unique status — first as the impetus for the empowering of the FDA in 1962, now as a major factor pushing for a stripping away much of that power — will continue for the foreseeable future.

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<sup>122</sup>Id.

<sup>123</sup>Liz Skinner, The FDA: It’s Broke, Warfield’s Business Record, Apr. 29, 1996, available in 1996 WL 8797809.

<sup>124</sup>Labor Changes In FDA: Hearings on S. 1477 Before the Senate Comm. on Labor and Human Resources, 104<sup>th</sup> Cong. (1996) (statement of FDA Commissioner Kessler), available in 1996 WL 7135603.

<sup>125</sup>142 Cong. Rec. S3203-01 (1996) (statement of Senator Kennedy).