From Tragedy to Triumph:
The Approval of Thalidomide"

by Kristina E. Lutz

"Can we learn from this lesson, or can mankind educate itself only by disaster and tragedy?"

–Sen. Paul Douglas, on the acceptance of the Senate's 1962 drug bill.[1]

In the late 1950s and early 1960s the drug thalidomide sent shock waves around the world when it was proven that the purportedly harmless drug, given to pregnant mothers as a sedative to combat morning sickness, was the cause of debilitating birth defects. While more than 8000 children worldwide were born with such thalidomide deformities as flipper-like arms and legs,[2]the United States escaped practically unscathed due to the diligence of one FDA medical reviewer, Frances O. Kelsey. The persistence of Dr. Kelsey ensured that the drug was never approved for mass American distribution. Nearly four decades after what has been called "the greatest drug tragedy of our time," [3]$on July 16, 1998, the federal Food and Drug Administration made history when it approved thalidomide for the tre$ the New Drug Application (NDA) of a little known drug company, the New Jersey-based Celgene Corporation, FDA released the known teratogen[5]to the American medical community under the strictest restrictions

[1]Harvey Teff & Colin R. Munro, Thalidomide: The Legal Aftermath 111 (1976), quoted in R. Harris, The Real Voice 215 (1964).

[2]The scientific name of these deformed limbs is phocomelia. See generally Stuart L. Nightingale, From the Food and Drug Administration, 280 J. Am. Med. Ass'n 872, 872 (1998).

[3]Pamela R. Ferguson, Pharmaceutical Products Liability: 30 Years of Law Reform?, 1992 Jurid. Rev. 226, 226 (citing The Thalidomide Children and the Law, report by The Sunday Times (1973) London, Andre Deutsch, preface, p. 7).

[4]See Approval Letter of NDA 20-785 from Dr. Murray M. Lumpkin, Deputy Center Director (Review Management), Center for Drug Evaluation and Research of the Food and Drug Administration, to Steve Thomas, Celgene Corp. 1 (July 16, 1998) (visited March 26, 1999) <http://www.fda.gov/cder/news/thalinfo/thalidomide.htm> [hereinafter Approval Letter].

[5]A teratogenic agent is defined as an agent ''of, or relating to, or causing developmental malformations or monstrosities.'' Webster's Dictionary 1216 (9th ed. 1983).

in the history of the federal agency.

This paper analyzes the history of thalidomide and argues that the recent decision to approve the dangerous drug was not only correct but made easy by the approval of another teratogenic drug called isotretinoin (marketed under the brand name Accutane) and by the recent FDA policies supporting inclusion of women in clinical trials. Part I describes thalidomide's storied past: from European tragedy to American triumph and the direct effect the drug had on FDA's drug approval process. Part II discusses the recent medical findings of thalidomide's therapeutic effect on leprosy, cancer, and complications of AIDS, to name only a few. Part III details FDA's approval of thalidomide, focusing on the S.T.E.P.S.^{TM} Program instituted by Celgene as an effort to prevent as many thalidomide birth defects as possible. Part IV, as stated above, analyzes FDA's decision itself, and argues that the decision was made uncontroversial by specific events in FDA history.

I. Thalidomide's Turbulent History

Thalidomide, an off-white, nearly odorless, and crystalline powder,[6] first appeared in Germany in 1953. The discoverer, a West German company called Ciba, discarded the drug after it was found to have no pharma-

[6] See David Stirling et al., Thalidomide: A Surprising Recovery, NS37 J. Am. Pharmaceutical Ass'n 306, 308 (1997).

cological effect in animals.[7]A few years later, however, thalidomide experienced a rebirth when another West German company, Chemie Grünenthal, found that it worked as a hypnotic, producing a deep sleep without hangover.[8]Claiming that the drug was "completely non-poisonous" and "completely safe," the company launched thalidomide under the name *Contergan* on October 1, 1957.[9]

Contergan soon became the sedative of choice in West Germany. In fact, by the end of the first year, Grünenthal was selling an amazing 90,000 packets of the drug a month.[10]Much of the popularity was due to the availability of the drug (it was inexpensive and available without a prescription) and the drug company's 1958 advertising campaign.[11]The company intentionally set out to promote the alleged safety of the product. For instance, in an August, 1958 letter to West German general practitioners, Grünenthal promoted the use of *Contergan* by pregnant mothers: "In pregnancy and during the lactation period, the female organism is under great strain. Sleeplessness, unrest, and tension are constant complaints. The administration of a sedative and hypnotic that will hurt neither mother nor child is often necessary."[12]Despite the claim that *Contergan* "[did] not damage either mother or child," the drug company had never tested thalidomide on any pregnant animals.[13] Grünenthal exported *Contergan* to forty-two countries worldwide and negotiated numerous manufacturer licenses to allow for the foreign production

[7]See id.; Max Sherman & Steven Strauss, Thalidomide: A Twenty-Five Year Perspective, 41 Food Drug Cosm. L.J. 458, 459 (1986).

[8]See Stirling et al., supra note 6, at 308; Richard E. McFadyen, Thalidomide in America: a Brush with Tragedy, 11 Clio Medica 79, 79 (1976).

[9]The Insight Team of The Sunday Times of London, Suffer the Children: The Story of Thalidomide 29-30 (1979).

[10]See id. at 30.

[11]See McFadyen, supra note 8, at 79.

[12]See Teff & MUNRO, supra note 1, at 1.

[13]Id. at 2.

of thalidomide.[14]Anxious to exploit the American market, Grünenthal approached both Smith, Kline & French, and Lederle before finally successfully securing Vick Chemical Company (Richardson-Merrell), ^{15}*the parent of William S. Merrell Company known for Vicks VapoRub, as its American licensee.*[16] At the time, Richardson-Merrell knew nothing about thalidomide yet they planned to promote the drug as a panacea; the company expected to cure anxiety associated with a panoply of afflictions that included cancer, tuberculosis, menopause, alcoholism, poor school work, and even marital discord.[17] Thalidomide's "investigational" period in the United States began on February 11, 1959 when Richardson-Merrell sent the drug to an unsuspecting medical community for human experimental use.[18]The company had not engaged in prior animal testing yet the physicians were assured that the drug was safe.[19]By May, pregnant women were given the drug.[20]Even by the relaxed standards of the time, the "trials" themselves were controversial. The investigational program was operated through Richardson-Merrell's sales, not medical, division, placebos were distributed only after a participating physician specifically requested them, and no other company had ever relied on more than 5,000 test subjects (whereas 20,000 American subjects took thalidomide).[21]In the months following the

[14]See The Insight Team, supra note 9, at 29.

[15]Vick changed its name to Richardson-Merrell Inc. in 1960. See id. at 64. For purposes of this paper, the company will be referred to as Richardson-Merrell.

[16]On a rather telling note, Richardson-Merrell also manufactured the ill-fated Mer 29, or Triparanol, a drug claimed to lower cholesterol. See id. at 64-64. Soon after its introduction to the market, appalling side effects, such as vomiting, loss of hair, nausea, and eye damage, were reported. See id. at 65-66. Then, in 1962, a leak to the FDA exposed Richardson-Merrell's illegal investigating practices on Mer 29. See id. at 66-67. After the drug company and individual officers were indicted on criminal charges, a federal judge ordered the company to pay a fine of $80,000 and sentenced the individual officers to six months probation. See id. at 67-68. Additionally, it is estimated that the drug company paid over $200 million in the nearly 500 civil lawsuits that followed. See id. at 68.

[17]See id. at 68.

[18]See id. at 69.

[19]See id.

[20]See id.

[21]See id. at 70-71.

tragedy, it was found that a total of 2,528,412 thalidomide tablets had been sent to 1,267 doctors across the country.[22] Frances Oldham Kelsey arrived at the Food and Drug Administration just one month before Richardson-Merrell's thalidomide application.[23]Fresh from Vermillion, South Dakota where she had spent three years practicing general medicine, the University of Chicago-trained physician and pharmacology Ph.D. spent her first month in an orientation program learning about the agency's general practices.[24]Once back in the New Drug Branch of the Bureau of Medicine (now the Center for Drug Evaluation), Kelsey's superiors decided to assign their newest medical officer what they considered a straightforward application.[25]It was under these auspices that on September 12, 1960, Dr. Kelsey was introduced to Richardson-Merrell's thalidomide product, *Kevadon*.[26] At the time of the application's submission there had not been any reports of problems pertaining to thalidomide.[27]Although it would be later proved that the first thalidomide baby was born on Christmas day, 1956 in Stolberg, Germany,[28]European doctors had yet to make the connection between the horrible birth defects and thalidomide.

Before *Kevadon* could be marketed, the 1938 Food, Drug and Cosmetic Act required Richardson-Merrell to prove to FDA that their drug was safe.[29]FDA had a sixty-day window of time to review the application and to contact the drug company if safety problems or questions arose.[30]If FDA failed to contact the

[22]See id. at 70.

[23]See Frances O. Kelsey, Thalidomide Update: Regulatory Aspects, 38 Teratology 221, 221 (1988).

[24]See id; THE INSIGHT TEAM, supra note 9, at 73; McFadyen, supra note 8, at 80.

[25]See Kelsey, supra note 23, at 221; McFadyen, supra note 8, at 80.

[26]See Kelsey, supra note 23, at 221; McFadyen, supra note 8, at 80.

[27]See Sherman & Strauss, supra note 7, at 460.

[28]See Widukind Lenz, A Short History of Thalidomide, 38 Teratology 203, 204 (1988). The father of the first thalidomide baby worked for Chemie Grünenthal. See id. The man had secured some samples of Contergan for his wife. See id. Their daughter was born without ears. See id.

[29]See 21 U.S.C. §355(b) (1958).

[30]See id. at §355(c).

drug sponsor by the sixtieth day, then the New Drug Applications automatically became effective.[31]If FDA found the NDA incomplete, then the applicant manufacturer was notified of the deficiencies and, because technically the application was not accepted for filing, the applicant was allowed to submit supplemental information to correct the application.[32]The NDA was regarded as withdrawn and resubmitted, giving FDA a new sixty-day review period.[33] This statutory framework played a central role in Dr. Kelsey's attempt to keep *Kevadon* off the market. From the beginning, Kelsey was troubled by the application, finding that the "claims were just too glowing—too good to be true," and that the clinical reports were "really more testimonials than scientific studies."[34]With these concerns in mind, Kelsey effectively put a halt to the drug's manufacture by penning a letter to Richardson-Merrell on November 10, 1960, only two days before the end of the sixty-day statutory review period. Had Kelsey not contacted the drug company, *Kevadon's* NDA would have automatically become effective pursuant to the provisions of the 1938 Food, Drug and Cosmetic Act.[35]This letter, which found the *Kevadon* NDA incomplete and outlined it's inadequacies,[36]in effect gave FDA an additional statutory review period and required Richardson-Merrell to provide FDA with more information if the drug company wanted to market thalidomide. The November 1960 letter, the first of five

[31]See id.

[32]See id.

[33]See supra notes 34-38 and accompanying text.

[34]McFadyen, supra note 8, at 80 (citing Dr. Frances O. Kelsey, oral history interview held at the offices of the Food and Drug Administration, Rockville, Maryland, May 30, 1974).

[35]See 21 U.S.C. §355(c) (1958) (providing that an NDA ''shall become effective on the sixtieth day after the filing thereof unless prior to such day the Secretary by notice to the applicant in writing postpones the effective date of the application....'').

[36]The stated inadequacies included: 1) insufficient reporting of the animal studies; 2) insufficient reporting of the clinical studies; 3) incomplete chronic toxicity data; 4) insufficient information on Chemie Grünenthal's manufacturing and testing methods; 5) limited information about Kevadon's stability; 6) minimal treatment of side effects; 7) no data to support the claim that expectant mothers suffering from nocturnia (excessive passing of urine in the night) had no difficulty arising at night or returning to sleep when using thalidomide. See Interagency Coordination in Drug Research and Regulation: Hearings Before the Subcomm. on Reorganization and Int'l Org. of the Senate Comm. on Gov't Operations, 87th Cong. 81-83 (1962) (letter from Dr. Frances O. Kelsey, FDA, to Dr. F.J. Murray, William S. Merrell Co.) [hereinafter Thalidomide Hearings]; see also The Insight Team, supra note 9, at 74.

such "application incomplete" letters that FDA would send over the course of the next year,[37]marked the beginning of the tumultuous relationship between FDA's most junior medical officer and one of America's medical giants.[38] In February 1961, Kelsey discovered a letter by Dr. A. Leslie Florence in the December 31, 1960 issue of the *British Medical Journal* suggesting that prolonged use of thalidomide resulted in peripheral neuritis.[39]Angered by the fact that Richardson-Merrell had failed to disclose the side effect, Kelsey requested further animal studies, clinical information, and a list of all of the clinical investigators who had been given *Kevadon*.[40] Reluctantly, Richardson-Merrell representatives traveled to Germany to meet with Grünenthal about the link between peripheral neuritis and thalidomide.[41]Grünenthal told Richardson-Merrell's Dr. F.J. Murray that the side effects were reversible: in all of the only thirty-four cases in West Germany, the symptoms faded once the patient stopped taking the drug.[42]This report, like the many others from Richardson-Merrell that crossed Kelsey's desk, were read with a great deal of suspicion. Later, Kelsey commented that she "had the feeling throughout that [Richardson-Merrell was] at no time being wholly frank with me."[43]Her skepticism was for good reason: Grünenthal in fact knew of 400 cases of peripheral neuritis, many of which were *not* reversible.[44] The situation escalated again in April when Dr. Murray contacted Dr.

[37]From November 1960 to March 1962, FDA sent five letters to Richardson-Merrell finding the Kevadon NDA incomplete and inadequate, and four letters stating that the NDA was considered withdrawn and resubmitted. See Thalidomide Hearings, supra note 36, 75-81.

[38]Kelsey later recalled her dealings with Richardson-Merrell: ''Whereas other firms had on occasion applied pressure, in no instances was it as severe as with this application.'' McFadyen, supra note 8, at 80 (citing Memo of Meeting between President Richardson-Merrell and Frances O. Kelsey, Aug. 13, 1962, FDA Files 520.T15X Aug. - Aug. 31, 1962).

[39]See Teff & Munro, supra note 1, at 5; McFadyen, supra note 8, at 81; The Insight Team, supra note 9, at 76. Peripheral neuritis is marked by the loss of sensation of the nerves in the hands and feet. See infra Part II F and accompanying notes.

[40]See The Insight Team, supra note 9, at 76.

[41]See id. at 77.

[42]See id.

[43]Id. at 78; McFadyen, supra note 8, at 81.

[44]See The Insight Team, supra note 9, at 77.

Kelsey's supervisor alleging that the company would be contacting the FDA Commissioner because Kelsey was unreasonably avoiding a decision on whether or not the *Kevadon* NDA was complete.[45]Murray then wrote to Dr. Kelsey demanding a final decision and stating, "I again want to stress that there is actually no proof thalidomide causes peripheral neuritis. The evidence is circumstantial."[46]Kelsey's May 5, 1961 response informed Murray once again that the application was incomplete and inadequate and boldly accused the company of deliberately hiding information from FDA:

[45]See id. at 78.

[46]Id.

> On the present evidence we cannot regard *Kevadon* tablets as safe in the sense that its usefulness as a sedative hypnotic outweighs the toxic effects indicated by the cases of peripheral neuritis.... The burden of proof that the drug is safe—which must include adequate studies of all the manifestations of toxicity which medical or clinical experience suggest—lies with the applicant. In this connection we are much concerned that apparently evidence with respect to the occurrence of peripheral neuritis in England was known to you but not forthrightly disclosed in the application.[47]

Incensed over what he called a "somewhat libelous" letter,[48]Murray set up another meeting with Dr. Kelsey. There, for the first time, Kelsey requested proof that Kevadon was safe for use during pregnancy.[49]

Peripheral neuritis continued to be Kelsey's primary concern since the investigator was unaware of the link between thalidomide and the unusual outbreak of birth defects in Europe. Unbeknownst to FDA and Richardson-Merrell, foreign scientists were beginning to draw the connection between the drug and children born with flipper-like limbs and missing fingers, toes, and ears.

Although Australian obstetrician William McBride is credited as one of the first to implicate thalidomide, his thin proof caused the global scientific community to dismiss his message.[50]In June 1961, McBride discovered that of the three malformed babies he had recently delivered all of the mothers had taken *Distaval*, the thalidomide brand name in Britain.[51]Convinced that *Distaval* was to blame, the doctor contacted the drug's Australian manufacturer,[52]sent a paper to Britain's medical journal *The Lancet*,[53]and began animal studies

[48]See id.; McFadyen, supra note 8, at 82.

[49]See Thalidomide Hearings, supra note 36, at 79; see also The Insight Team, supra note 9, at 79; McFadyen, supra note 8, at 82.

[50]The New South Wales Medical Tribunal found William McBride guilty of scientific fraud concerning his use of caesareans in pregnant women and banned him from the practice of medicine. For McBride's version of the charges and the trial, see William McBride, Killing the Messenger (1994).

[51]See The Insight Team, supra note 9, at 86; Anthony H. Lipson, Thalidomide Retrospective: What Did the Clinical Teratologist Learn, 46 Teratology 411, 411 (1992).

[52]See The Insight Team, supra note 9, at 87.

[53]See id. at 88.

to replicate the effects he had witnessed in humans.[54]The next three months proved frustrating for McBride: the manufacturer, DCBAL, refused to believe his claims, he was unable to produce the same deformities in mice and guinea pigs, 23 women who had taken thalidomide during their pregnancy gave birth to normal children, and *The Lancet* rejected McBride's paper for publication.[55]

The link between thalidomide and phocomelic birth defects was under investigation in Germany also in June 1961. At that time a young lawyer named Karl Shulte-Hillen contacted Professor Widukind Lenz, the Assistant at the Children's Clinic at Hamburg University.[56]Both Shulte-Hillen's wife and sister had recently given birth to babies with shrunken arms and missing fingers and the lawyer theorized that something in his hometown was responsible for the birth defects.[57]Although Lenz discounted Shulte-Hillen's theory, he began counting the number of phocomelic cases and found that while there had only been one recorded case between 1930 to 1955, there were a record fifty between September 1960 and October 1961.[58]Still missing the common thread, Lenz interviewed the mothers of the affected children hoping that they might provide insight into the causal agent.[59]The Hamburg doctor fortuitously stumbled upon the answer when on November 11, 1961 one of his subjects described an intake of thalidomide before and during her pregnancy, the peripheral neuritis she experienced, and her concern throughout the pregnancy that the drug might be harming her

[54]See id.

[55]See id. at 91. It later would be proven that a pregnant woman could ingest thalidomide at certain times during pregnancy without harming her child. Specifically, birth defects would result only if a woman took thalidomide 36 to 50 days following her last menstrual period, or 22-36 days after conception. See infra note 98 and accompanying text.

[56]See id. at 96; Lipson, supra note 51, at 211.

[57]See The Insight Team, supra note 9, at 96-97; Lipson, supra note 51, at 211.

[58]See The Insight Team, supra note 9, at 97-98; Lipson, supra note 51, at 211.

[59]See The Insight Team, supra note 9, at 98; Lipson, supra note 51, at 212.

child.[60]The next day four other mothers told Lenz of their thalidomide use, and by November 15 fourteen more cases were recorded.[61]Lenz immediately contacted Grünenthal.

Throughout this time, McBride had continued his Australian crusade against thalidomide. After two more babies with phocomelia were born in September 1961 to mothers who had taken *Distaval* early in their pregnancies, McBride spent another two months pressuring DCBAL.[62]It wasn't until late November that the drug company finally agreed to meet with the obstetrician.[63]In what proved to be fortunate timing, a report of McBride's findings arrived in Germany just after Lenz presented his damning research to Grünenthal.[64]

Despite the evidence from across the globe, Grünenthal executives were still reluctant to withdraw their money-making wonder drug. In a weekend meeting, the company leaders opted only to notify doctors and pharmacists of the Lenz data.[65]Their decision was preempted the next day, when on November 26, 1961 the headline of the German newspaper *Welt am Sonntag* screamed "Malformations from tablets—alarming suspicion of physician's globally distributed drug."[66]Grünenthal was forced to withdraw *Contergan* from the market that same day.[67]News of the German event reached Dr. Kelsey on November 30, 1961 when

[60]See The Insight Team, supra note 9, at 98; Lipson, supra note 51, at 212.

[61]See The Insight Team, supra note 9, at 98; Lipson, supra note 51, at 212.

[62]See The Insight Team, supra note 9, at 92-93.

[63]See id. at 93.

[64]See id. at 103.

[65]See id.

[66]See id. at 104. While Lipson believes that either Dr. Lenz, Schulte-Hillen or the German Health Bureaucracy in fact leaked the thalidomide story to the Welt am Sonntag, see Lipson, supra note 51, at 412, Lenz himself suspects the Düsseldorf Ministry of the Interior. See Widukind Lenz, A Personal Perspective on the Thalidomide Tragedy, 46 Teratology 417, 418 (1992). Lenz recounts how the international press mistakenly reported that the Düsseldorf Ministry of the Interior had prohibited the sale of thalidomide. See id. While the drug's name had not been mentioned in the German newspaper account, the mistake fortunately could not be corrected in time in the foreign press. See id.

[67]See id.

Richardson-Merrell reported to her the possibility that thalidomide was causing appalling birth defects.[68] At first, FDA was hesitant to blame thalidomide. Kelsey later claimed: "In *any* adverse reaction report like this there *always* is a period of doubt where you're not sure that this *is* the real correlation. We were aware that this drug was in the investigational stage. We felt perhaps wrongly... that it was well under control of the sponsors."[69]However, little doubt remained after Kelsey and an FDA colleague met with Dr. Helen Taussig, a Pediatrics professor at the Johns Hopkins University School of Medicine, in April 1962.[70]Dr. Taussig had contacted FDA after returning from Europe to report her firsthand knowledge of the widespread and devastating effects caused by thalidomide.[71]Taussig was the first to describe to Kelsey the "seal limbs" of the European children she encountered and how a number of European researchers felt that thalidomide was to blame.

Armed with this new knowledge, Kelsey wrote to Richardson-Merrell to determine whether *Kevadon* was still in investigational use.[72]Throughout the *Kevadon* application's review, FDA presumed that only thirty-five to sixty clinical investigators had been working with thalidomide.[73]Kelsey was therefore shocked to learn at the end of April that Richardson-Merrell had sent the drug to over 1,000 doctors.[74] After meeting with Kelsey, Dr. Taussig worked quickly to warn the American medical community. In mid-April 1962 Taussig described the birth defects of the thousands of European children to a meeting of the American College of Physicians.[75]While a *New York Times* article covering the meeting was largely ignored by the American

[68]See McFadyen, supra note 8, at 82-83.

[69]Id. at 83.

[70]See Kelsey, supra note 23, at 221; McFadyen, supra note 9, at 83.

[71]See Kelsey, supra note 23, at 221; McFadyen, supra note 9, at 83.

[72]See McFadyen, supra note 8, at 84.

[73]See id.

[74]See id.

[75]See id.

public, it was embraced by lawmakers in Washington.

Since 1959, Senator Estes Kefauver (D-TN) had been investigating the American drug industry in the hopes of reducing drug prices.[76]The history of drug regulation in this country is a troubled one. The Federal Food and Drugs Act of 1906 allowed companies to market drugs without government examination but permitted what was then the U.S. Department of Agriculture's Bureau of Chemistry to seize an adulterated or misbranded drug already in the stream of commerce.[77]Comprised of a confusing amalgamation of rules, the archaic statute permitted drug manufacturers to deviate from nationally established purity and quality standards so long as the individual standard was printed on the drug's label.[78]Following the 1937 "Elixir Sulfanilamide" tragedy which killed 107 people, the Federal Food, Drug, and Cosmetic Act of 1938 was enacted requiring FDA drug safety approval before marketing.[79]The limitations of the 1938 Act soon became apparent. For instance, since the Act only required the drug to be "safe," any effectiveness claims were the manufacturer's responsibility.[80]Furthermore, the exemption for new drugs in clinical investigations allowed the manufacturer to proceed virtually unmonitored. The drug sponsor was not required to notify FDA of human testing and the manufacturer was only required to report the trial results if a new drug application was submitted.[81] Congressional hearings in late 1959 on the pricing and promotional practices of the drug industry produced Sen. Kefauver's bill, S.1552, which as originally submitted was an attack on high drug

[76]See id.

[77]See Peter Barton Hutt & Richard A. Merrill, Food and Drug Law: Cases and Materials 4, 9 (2nd ed. 1991)(reprinting Lauffer Hayes & Frank Ruff, The Administration of the Federal Food and Drugs Act, 1 Law and Contemp. Probs. 16 (1933)).

[78]See id. at 9.

[79]See Kelsey, supra note 23, at 222.

[80]See id.

[81]See id.

prices.[82]After further hearings, the bill was radically amended and resubmitted out of the Subcommittee on Antitrust and Monopoly on March 8, 1962.[83]The focus of the amended S.1552 shifted from curbing exorbitant drug prices to strengthening the Federal Food, Drug and Cosmetic Act of 1938 by requiring, among other things, that a drug manufacturer provide information on a drug's effectiveness as well as it's safety.[84]Over the next few years S.1552 sat lame in committee but was given new life by the 1962 *New York Times* article on Dr. Taussig's presentation to the American College of Physicians.[85]Soon, Taussig was testifying in front of Congress and a few months later the *Washington Post* broke the thalidomide story to the American public.[86]Thalidomide, Dr. Kelsey, and the lack of FDA controls over experimental drugs became front-page news.

The popular press's coverage of the teratogenic drug increased the pressure on FDA to locate all of the samples Richardson-Merrell had distributed during its "investigational" studies. During a nationwide recall, it was discovered that of the more than five tons of thalidomide that Richardson-Merrell had initially received, over two tons were still at large and could not be located through the drug company's spotty records.[87]Richardson-Merrell and FDA set out to track down the remaining doses of the drug and even President John F. Kennedy became involved when he urged Americans during a press conference to check their medicine cabinets for thalidomide.[88] Following the completion of the drug's recall, FDA determined that seventeen thalidomide

[82]See Kelsey, supra note 23, at 222.

[83]See S. Rep. No. 87-1744 (1962).

[84]See id. The amended S.1552 also proposed modifications in the length of exclusive drug patents as well as proposing a drug manufacturers registry with HEW, factory inspection, manufacturing controls, record and reporting requirements for clinical investigations, labeling and official drug name changes, and antibiotic certification. See id. Further amendments (including provisions for the new approval process) were made before Congress passed it under the name ''Drug Amendments of 1962.''

[85]See Robert K. Plumb, Deformed Babies Traced To A Drug, N.Y. Times, April 12, 1962, at 37.

[86]See Morton Mintz, Heroine of FDA Keeps Bad Drug Off Market, Wash. Post, July 15, 1962, at A1.

[87]See McFadyen, supra note 8, at 85.

[88]See id.

children had been born in the United States.[89]While seven of the mothers had acquired the drug overseas, the remaining ten had been affected by the Richardson-Merrell distribution.[90]In subsequent years, it was clear that the United States had escaped tragedy. Nations around the globe reported shocking statistics: 3,049 thalidomide births in Germany, more than 300 in Japan, 271 in the United Kingdom, 122 affected Canadian children, and thousands more from other countries.[91] The thalidomide ordeal was directly responsible for positive change in this country. For one, Sen. Kefauver's efforts, although originally aimed at reducing drug prices, drew attention to the inadequacies of the drug approval process. Recognizing the need for tighter agency control, Congress passed a greatly amended version of S.1552 in what became known as the Kefauver-Harris Amendments or the Drug Amendments of 1962.[92]In final form, the Amendments changed the approval process, added an effectiveness requirement, and mandated record-keeping. Specifically, by requiring explicit FDA authorization before a manufacturer is allowed to introduce a drug into interstate commerce, the Amendments eradicated the automatic sixty-day approval process that had bound Dr. Kelsey.[93]The new law also permitted FDA to withdraw approval if new evidence not contained in the application was found to be an "imminent hazard to the public health."[94]Furthermore, manufacturers were required to prove not only the safety of the drug product but also the effectiveness under the stated conditions and uses.[95]Data from clinical trials had to be recorded and the manufacturer was obligated to report immediately any adverse

[89]See id. at 86

[90]See id.

[91]Widukind Lenz, A Short History of Thalidomide Embryopathy, 38 Teratology 202 passim (1988).

[92]Pub. L. No. 87-781, 76 Stat. 780 (1962).

[93]See Drug Amendments of 1962, Pub. L. No. 87-871, 76 Stat. 780, 784 (codified as amended at 21 U.S.C. §355(a)).

[94]See id., 76 Stat. at 782 (21 U.S.C. at §355(e)).

[95]See id., 76 Stat. at 781 (21 U.S.C. at §355(b)).

conditions attributable to the drug product.[96]Since many of the Americans taking thalidomide as part of Richardson-Merrell's clinical trials were unaware of the drug's investigational status, the Amendments required manufacturers, with limited exceptions, to inform patients of the study and to secure their consent to take an experimental drug.[97] Thalidomide is also responsible for the development of teratology as a field of study. In the years following the tragedy, researchers were able to pinpoint the critical period of exposure. Phocomelia resulted only if the mother ingested thalidomide thirty-six to fifty days following her last menstrual period, or twenty-two to thirty-six days after conception.[98] Finally, as for the woman credited with fending off an American drug giant and saving thousands of babies from devastating birth defects, President John F. Kennedy awarded Dr. Kelsey with the Gold Medal Award for Distinguished Federal Civilian Service.[99]

II. Thalidomide's Resurgence.

In a surprising 1965 article, an Israeli doctor reported the remarkable effects thalidomide had had in alleviating complications of leprosy. Since then, through controlled clinical trials and FDA compassionate-use programs, the drug has been found to be effective in treating a myriad of disorders, including certain

[96]See id., 76 Stat. at 782-83 (21 U.S.C. at §355(k)(1)).

[97]See id., 76 Stat. at 783 (21 U.S.C. at §355(i)).

[98]See Robert L. Brent & Lewis B. Holmes, Clinical and Basic Science Lessons From the Thalidomide Tragedy: What Have We Learned About the Causes of Limb Defects?, 38 Teratology 241, 242-43 (1988).

[99]See McFadyen, supra note 8, at 90.

mycobacterial and autoimmune diseases, HIV and AIDS-related afflictions, cancer, and miscellaneous skin conditions.

A. Microbacterial Diseases

Approximately ten to fifteen million people worldwide suffer from leprosy, or Hansen's Disease, a chronic disease of the skin and peripheral nervous system.[100]Although more common in Africa, India, Southeast Asia, and Brazil, this greatly misunderstood disease is indigenous to certain parts of the United States and, according to 1992 statistics, affects more than 7,000 Americans.[101] There are two main forms of leprosy: tuberculoid and lepromatous.[102]The symptoms of the former include an enlarged nerve near a solitary lesion which can arise anywhere on the body whereas the latter manifests itself in dry, cracked skin, numerous lesions all over the body, and eventual hand and feet deformities.[103]Once treatment begins, patients respond to the leprosy antigens by experiencing what are called "lepra reactions," of which there are two types.[104]In type 1 lepra reaction, commonly associated with tuberculoid leprosy, the skin lesion simply becomes inflamed.[105]However, in type 2, found in lepromatous leprosy sufferers, red nodular lesions appear in clusters all over the body, arms and legs may swell, eyesight worsens, and fever, weight loss, arthritis, and general malaise may occur.[106]This type 2 lepra reaction is called erythema nodosum leprosum,

[100]See Sharon M. Martin & Graeme J. Kutt, Leprosy: Medieval Myth or Modern Menace?, 7 Clinical Laboratory Sci. 283, 283 (1994).

[101]See Alec Style, Early Diagnosis and Treatment of Leprosy in the United States, 52 Am. Fam. Physician 172, 172 (1995).

[102]See Mitchell S. Meyerson, Erythema Nodosum Leprosum, 35 Int'l J. Dermatology 389, 389 (1996).

[103]See Style, supra note 101, at 173-74.

[104]See id. at 176.

[105]See id.

[106]See id.

or ENL. Studies report that while between 15 and 50% of lepromatous leprosy patients develop ENL within the first year of treatment, the reaction can develop after the first year and even after treatment has been discontinued.[107] In 1965 Israeli dermatologist Jacob Sheskin accidentally discovered that thalidomide rapidly alleviated ENL symptoms.[108]Following the ingestion of thalidomide, the lesions of six patients, all of whom suffered from the lepromatous form of leprosy, showed significant clearing after a mere twenty-four to forty-eight hours.[109]The dermatologist then embarked on a fifteen-year worldwide study that included 4522 ENL patients.[110]The results were remarkable: 99% showed improvement with thalidomide treatment.[111]Sheskin also noted the remission of other side effects such as headache, anorexia, and vomiting.[112] Shortly after the publication of Sheskin's 1965 study, FDA approved the clinical study of thalidomide at the National Hansen's Disease Center in Carville, Louisiana and in 1975 the US Public Health Service set up a compassionate use program to distribute the drug to Hansen's Disease patients.[113]The results of these long-term studies would later facilitate thalidomide's move from experimental to approved status.[114] Recently, researchers have begun to test thalidomide's effectiveness in tuberculosis (TB). The oldest documented infectious disease, TB continues to cause about three million deaths per year and affects an estimated one billion people

[107]See Meyerson, supra note 102, at 389.

[108]See generally Jacob Sheskin, Thalidomide in the Treatment of Lepra Reactions, 6 Clinical Pharmacological Therapy 303 (1965).

[109]See id. at 306.

[110]See Jacob Sheskin, The Treatment of Lepra Reaction in Lepromatous Leprosy: Fifteen Years' Experience with Thalidomide, 19 Int'l J. Dermatology 318, 319 (1980).

[111]See id.

[112]See id. at 320.

[113]Participants of this study were limited to male and post-menopausal women. If a woman of childbearing potential wished to be included in the trial, she had to be surgically sterilized or hospitalized at the Carville center for the entire period of thalidomide therapy and undergo weekly pregnancy testing. See Dr. Leo Yoder, Remarks at The 47th Dermatologic and Opthalmic Drugs Advisory Committee Meeting (Sept. 4, 1997) (transcript available at <http://www.fda.gov/dockets/com97me/transcri/3321tl.txt>.

[114]See infra Part III.

worldwide.[115]In 1991, a team of Rockefeller University scientists discovered that thalidomide aided the immune system by suppressing a protein responsible for inflammation called tumor necrosis factor-alpha (TNF-alpha).[116]Once researchers determined that increased TNF-alpha was present in patients with TB and ENL, they hypothesized that thalidomide would treat both diseases effectively.[117]Confirming this theory, a 1995 study including thirty tuberculosis-infected men in Thailand and New York reported a decrease in the patients' adverse blood condition.[118] B. HIV and AIDS-related disorders

The combination of the Rockefeller findings and the discovery that patients with HIV possessed increased levels of TNF-alpha led researchers to test the efficacy of thalidomide on HIV and AIDS-related disorders. Preliminary success has been found in cachexia (or wasting syndrome), recurrent aphthous ulceration, and Kaposi's Sarcoma.

Cachexia, or HIV wasting syndrome, is a common manifestation of AIDS involving involuntary weight loss plus either chronic diarrhea or chronic weakness and fever.[119]It is estimated that 50,000 - 100,000 Americans (or 50% of AIDS patients) suffer from cachexia during their battle with AIDS and, because of

[115]See Gilla Kaplan and V.H. Freedman, The role of cytokines in the immune response to tuberculosis, 147 Res. in Immunology 565, 565 (1996).

[116]See E.P. Sampaio et al., Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes, 173 J. Experimental Med. 699 (1991). High levels of TNF-alpha result in weight loss, muscle weakness, night sweats, and tissue deterioration. See Gilla Kaplan, Cytokine Regulation of Disease Progression in Leprosy and Tuberculosis, 191 Immunobiology 564, 566 (1994). Aside from TNF-alpha suppression, thalidomide is believed to affect the number of white blood cells in what is known as the CD4+:CD8+ ratio. See Meyerson, supra note 102, at 390. This ratio consists of the number of what are called helper/inducer T cells (CD4+) to suppressor/cytotoxic T cells (CD8+). See id. In ENL patients, this ratio is abnormally increased. Simply stated, thalidomide has been shown to decrease this elevated ratio by reducing CD4+ cells and increasing the CD8+ cells. See id.

[117]See e.g., Gilla Kaplan, Cytokine Regulation of Disease Progression in Leprosy and Tuberculosis, 191 Immunobiology 564, 566 (1994).

[118]See J.M. Tramontana et al., Thalidomide treatment reduces tumor necrosis factor-$\forall$ production and enhances weight gain in patients with pulmonary tuberculosis, 1 Mol. Med. 387 (1995) (described in Gilla Kaplan, The role of cytokines in the immune response to tuberculosis, 147 Res. in Immunology 565, 569-70 (1996)).

[119]See Denise L. Balog et al., HIV Wasting Syndrome: Treatment Update, 32 Annals of Pharmacotherapy 446, 446 (1998).

the patient's inability to maintain normal body weight, the syndrome can lead to death.[120]The increased frequency of cachexia in recent years is believed to be the result of a longer AIDS survival rate.[121]The exact cause of cachexia is still unknown, although elevated TNF-alpha levels are present and may contribute to the weight loss.[122] Thalidomide has proven to aid weight gain in small clinical trials. For example, in a trial sponsored by the National Institute of Nutrition in Mexico City, researchers found that in a twelve-week trial of twenty-eight patients, eleven of the fourteen receiving thalidomide either gained weight or remained stable (79% efficacy) compared to four of fourteen in the placebo group (29%).[123]Similarly, another study reported a mean percentage body weight increase of 2.07% after one week and 3.06% after two weeks of thalidomide therapy in a trial of thirteen HIV-infected patients.[124]Presently, FDA has approved an expanded-access program for cachexia patients experiencing an involuntary loss of 20% or more body weight and for whom alternative treatments have failed.[125] Another complication of AIDS thought to be relieved by thalidomide is recurrent aphthous ulceration. The ulcers, appearing in about 3% of AIDS patients, may present themselves in the mouth, esophagus, or genital area.[126]Oral ulcers inhibit the patient's ability to eat and take medication, therefore wasting and malnutrition can occur.[127]One troubling aspect of the available

[120]See e.g., Celgene Corp., Thalomid: Aids---Related Conditions (visited March 26, 1999) <http://www.celgene.com/AIDS%20Related%20Conditions.htm>.

[121]See Gustavo Reyes-Terán et al., Effects of thalidomide on HIV-associated wasting syndrome: a randomized, double-blind placebo-controlled clinical trial, 10 AIDS 1501, 1505 (1996).

[122]See Balog et al., supra note 119, at 446-47.

[123]See Reyes-Terán et al., supra note 121, at 1503.

[124]See Patrick Haslett et al., The Metabolic and Immunologic Effects of Short-Term Thalidomide Treatment of Patients Infected with the Human Immunodeficiency Virus, 13 AIDS Res. and Human Retroviruses 1047, 1049 (1997).

[125]See James R. Minor & Stephen C. Piscitelli, Thalidomide in diseases associated with human immunodeficiency virus infection, 53 Am. J. Health-Sys. Pharm. 429, 429 (1996).

[126]See Susan C. Ball et al., Thalidomide for Treatment of Oral Aphthous Ulcers in Patients with HIV: Case Report and Review, 92 Am. J. of Gastroenterology 169, 169 (1997).

[127]See Jeffrey M. Jacobson et al., Thalidomide for the Treatment of Oral Aphthous Ulcers in Patients with HIV, 336 New Eng. J. Med. 1487, 1487 (1997).

corticosteroid treatment is the recurrence of the ulcers.[128] In 1997, an article in the *New England Journal of Medicine* reported that thalidomide is an effective treatment for aphthous ulceration of the mouth.[129]As part of a large AIDS Clinical Trials Group study (ACTG #251) the group of researchers found that the ulcers of 55% of the patients taking thalidomide completed healed within four weeks and 90% exhibited either complete or partial healing.[130]These results were compared to healed ulcers in only 7% of the placebo group, with 28% showing complete or partial healing.[131]Furthermore, patients reported that thalidomide alleviated the pain associated with aphthous ulcers and improved their ability to eat.[132] Despite the promising results described above, *The New England Journal of Medicine* article disclosed a disturbing result: thalidomide increased the patients' HIV-viral load.[133]Although earlier studies had found thalidomide to suppress TNF-alpha, the thalidomide-treated patients in this study actually experienced increased and higher levels of TNF-alpha than those in the placebo group.[134]Because increases in TNF-alpha enhance the production of HIV and the strength of the disease, the researchers discouraged the use of thalidomide in HIV-infected patients for longer than a two to four week period of time.[135] Thalidomide is also under investigation for the

[128]See id.

[129]See id. at 1491.

[130]See id. at 1489.

[131]See id.

[132]See id. at 1491. These results comport with an earlier ACTG study finding healed ulcers at four weeks in 14 of 23 (or 61%) patients on thalidomide, compared with healing in only 1 of 22 (or 4.5%) placebo-controlled patients. See Paul J. Weidle, Thalidomide for aphthous ulcers in patients infected with the human immunodeficiency virus, 53 Am. J. Health-Sys. Pharm. 368, 368 (1996).

[133]See Jacobson et al., supra note 127, at 1492.

[134]See id.

[135]See id. Subsequently, Dr. Debra Birnkrant of FDA chided Dr. Jacobson by reminding readers that half of Jacobson's participants either were discounted or received a dose reduction in the four-week study. See Debra Birnkrant, Thalidomide for Aphthous Ulcers in HIV Infection: Letter to the Editor, 336 New Eng. J. Med. 1086, 1086 (1997). She noted that Jacobson's findings of increased TNF-alpha warranted further investigation since the recent pharmacological emphasis had been on suppressing the protein. See id. at 1086-87.

treatment of Kaposi's sarcoma (KS), the cancerous lesions commonly associated with AIDS.[136]Prevalent in HIV-infected homosexual men,[137]the lesions, sometimes over a hundred in number, may appear anywhere on or in the body. While lesions on the skin are most common initially, they later appear in the mouth in approximately one-third of HIV patients and in the gastrointestinal tract in 40%.[138]Social isolation, anguish, and depression are common as a result of the unsightly lesions.[139] The study of thalidomide treatment for Kaposi's sarcoma is still young and researchers continue to recommend conventional available treatments like chemotherapy and radiotherapy.[140]A few researchers report efficacy in individual cases,[141]but others caution that the results may have arisen from mechanisms other than thalidomide.[142]

C. Autoimmune diseases

Thalidomide's ability to suppress TNF-alpha and affect other cell activity[143]has sparked scientific interest in the drug's ability to combat certain autoimmune diseases like lupus and rheumatoid arthritis. Currently, clinical trials are testing thalidomide's usefulness in lupus erythematosus, rheumatoid arthritis, and Crohn's

[136]See Susan E. Krown, Acquired Immunodeficiency Syndrome-Associated Kaposi's Sarcoma: Biology and Management, 81 Med. Clinics N. Am. 471, 484 (1997).

[137]Fifteen to twenty percent of HIV-infected homosexual men suffer from Kaposi's sarcoma compared with only 1-3% of other HIV sufferers other than homosexual men. See id. at 472.

[138]See id. at 474. Patients experiencing eating difficulty due to KS located on the gums, tongue, tonsils and surrounding areas may suffer from cachexia or AIDS wasting. See generally id. (discussing oral cavity KS leading to possible tooth loss and obstructed airways).

[139]See id.

[140]See e.g., Rolf A. Solèr et al., Regression of AIDS-Related Kaposi's Sarcoma During Therapy with Thalidomide, 23 Clinical Infectious Diseases 501, 503 (1996).

[141]See id. at 501 (reporting decrease in 14-year old girl's lesions with thalidomide treatment); see also M. Carlesimo et al., Treatment of cutaneous and pulmonary sarcoidosis with thalidomide, 32 J. Am. Acad. Dermatology 866 (1995)(describing thalidomide efficacy in treating case study KS).

[142]See e.g., Alexandra M. Levine, Editorial Response: Regression of AIDS-Related Kaposi's Sarcoma During Therapy With Thalidomide, 23 Clinical Infectious Diseases 504, 504-05 (1996).

[143]See supra, footnote 116.

disease.[144] Thalidomide's efficacy has been established in certain forms of lupus. Simply stated, there are two major forms of lupus: discoid lupus erythematosus (DLE), a generally mild, but sometimes chronic, form of the disease manifesting in a red, scaly rash usually located on the face, and systemic lupus erythematosus (SLE), the more common and severe form of lupus that includes rash, swelling of the joints, organ inflammation, and ulcers in the mouth or nose.[145]The effectiveness of thalidomide in DLE patients was established early in the 1980s[146]and the drug has shown similar promise for SLE. For example, a study of 23 SLE patients reported that 90% had complete remission with thalidomide treatment.[147] The drug has also shown some promise in small rheumatoid arthritis studies. For example, in an open study of seven female patients, thalidomide was found to relieve pain and joint inflammation in all cases.[148]Four of the women even enjoyed remission long after withdrawal of the drug.[149]Similarly, in a later thalidomide study

[144]See Stirling et al., supra note 6, at 311; Celgene Corp., Celgene Corp. Files SelCids™ Compound IND As Possible Treatment For Crohn's Disease (visited March 26, 1999) <http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=celg&script=410&layout=7&item_id=12710>.

[145]See Mayo Clinic, Lupus (visited March 26, 1999) <http://www.mayohealth.org/mayo/9605/htm/lupus.htm>. The third and very rare form of the disease, drug-induced lupus, will not be discussed in this paper. See e.g., Robert G. Lahita M.D., Lupus Foundation of America, Inc., Causes, Symptoms, Testing, Treatment (visited March 26, 1999) <http://www.internet-plaza.net/lupus/info/types.html>.

[146]See e.g., Stephanie Tseng et al., Rediscovering thalidomide: A review of its mechanism of action, side effects, and potential uses, 35 J. Am. Acad. Dermatology 969, 972 (1996) (noting results of two DLE studies: in one, thalidomide had a failure rate of less than 10%, most patients on thalidomide had results within two weeks, and 75% required maintenance therapy; the other study's authors reported peripheral neuropathic side effects and therefore recommended thalidomide treatment only after failure of conventional therapies); R.J. Stevens, The place of thalidomide in the treatment of inflammatory disease, 6 Lupus 257, 257 (1996). Recent studies conducted in London have confirmed these reports but note quick relapse upon drug withdrawal. See R.J. Stevens et al., Thalidomide in the Treatment of the Cutaneous Manifestations of Lupus Erythematosus: Experience in Sixteen Consecutive Patients, 36 Brit. J. Rheumatology 353, 354 (1997)(reporting that 44% of the patients experienced complete remission and 37% partial remission); see also Timothy Godfrey et al., Therapeutic advances in systematic lupus eythematosus, 10 Current Opinion Rheumatology 435, 436 (1998)(reporting that thalidomide induced complete remission in 60% DLE patients and partial remission in 30% with 75% relapse rate).

[147]See Tseng et al., supra note 146, at 972.

[148]See O. Gutierrez-Rodriguez et al., Thalidomide---A Promising New Treatment for Rheumatoid Arthritis, 27 Arthritis & Rheumatism 1118 (1984); see also Tseng et al., supra note 146, at 974.

[149]See Tseng et al., supra note 146, at 974.

involving seventeen patients, seven experienced complete remission and five partial remission.[150]

D. Cancer and Related Disorders

Aside from suppressing TNF-alpha, thalidomide prevents angiogenesis, the formation of new blood vessels.[151]This property, which was responsible for stunting the uterine limb growth of the 1950s and 60s thalidomide babies, may prove useful in combating breast and prostate cancer by preventing new tumor growth.[152]Preliminary results from the National Cancer Institute's prostate cancer study showed the drug stabilized the disease and lowered the PSA (or prostate-specific antigen) levels of all eighteen participants.[153]Presently, over 100 individual cancer patients use thalidomide on what FDA calls "an emergency basis."[154]

Thalidomide's antiangiogenesis properties have given researchers at Harvard Medical School and the University of Pennsylvania hope of using the drug for macular degeneration, a blinding eye disorder caused by harmful blood vessel growth and retinal bleeding.[155]The two institutions have teamed up to study the early stages of the disease in a small clinical trial.[156] Chronic graft-versus-host disease (CGvHD) is another

[150]See O. Gutierrez-Rodriguez et al., Treatment of refractory rheumatoid arthritis---the thalidomide experience, MEDLINE (OVID) Abstract, 16 J. Rheumatology 158 (1989).

[151]See A Cautious Comeback for Thalidomide, Harvard Health Letter, Feb. 1998, at 4.

[152]See e.g., Judith E. Karp et al., Prostate Cancer Prevention: Investigational Approaches and Opportunities, 56 Cancer Res. 5547, 5552 (1996) (stating that suppression of TNF-alpha production is one of the mechanisms of thalidomide's antiangiogenic action); Giampietro Gasparini & Adrian L. Harris, Clinical Importance of the Determination of Tumor Angiogenesis in Breast Carcinoma: Much More Than a New Prognostic Tool, 13 J. Clinical Oncology 765, 774 (1995) (listing thalidomide as an angiogenesis inhibitor).

[153]See Cancer Monitor, 14 Med. Malpractice L. & Strategy 6 (1997).

[154]See Stirling et al., supra note 6, at 312; Ann Saphir, Jekyll and Hyde: A New License for Thalidomide?, 89 J. Nat'l Cancer Inst. 1480, 1481 (1997).

[155]See A Cautious Comeback for Thalidomide, supra note 151, at 5.

[156]See id.

area of study. The disease, a complication of leukemia associated with bone marrow transplants, occurs in approximately 40% of patients who survive 100 days following their transplant.[157]Research shows that 52% of all patients with CGvHD do not survive.[158]Like many of the aforementioned disorders, the increased level of TNF-alpha in CGvHD sufferers led researchers to believe thalidomide would be an effective treatment.[159]Several studies have confirmed this hypothesis in chronic cases.[160]

E. Miscellaneous Skin Conditions

One final area of general thalidomide study involves special skin disorders, including Behçet's syndrome. Numerous individual case studies have found thalidomide useful in treating Behçet's disease, a multisystem disorder presenting oral and genital ulcers, arthritis, colitis, and painful lesions on the skin and eyes,[161]but not until last year were researchers able to replicate the results in a controlled trial. In that instance, a group from the Behçet's Syndrome Research Center in Istanbul, Turkey found thalidomide effective in suppressing existing oral and genital ulcers as well as preventing the formation of new ones.[162]Not surprisingly, the ulcers

[157]See Georgia B. Vogelsang et al., Thalidomide for the Treatment of Chronic Graft-Versus-Host Disease, 326 New Eng. J. Med. 1055, 1055 (1992).

[158]See id.

[159]See H.M. Lazarus & J.M. Rowe, New and Experimental Therapies for Treating Graft-versus-Host Disease, 9 Blood Reviews 117, 118 (1995).

[160]See e.g., Vogelsang, supra note 157, at 1057 (reporting overall survival rate of 64% or 28 of 44 patients taking thalidomide, complete eradication of disease in 14 patients, partial response in 12, and no response in 18 patients); Pablo M. Parker et al., Thalidomide as Salvage Therapy for Chronic Graft-Versus-Host Disease, 86 Blood 3604, 3606 (1995) (finding that thalidomide has activity against CGvHD evidenced by response of 16 of 80 patients).

[161]See e.g., Heidi C. Mangelsdorf et al., Behçet's disease, 34 J. Am. Acad. Dermatology 745, 750 (1996) (finding thalidomide effective in treatment of one patient's Behçet's lesions); Dongsik Bang, Treatment of Behçet's Disease, 38 Yonsei Med. J. 401, 405 (1997) (citing seven case studies in support of thalidomide efficacy for Behçet's mucocutaneous lesions, arthritis, and colitis); Tseng et al., supra note 146, at 973 (describing studies resulting in complete healing of oral and genital lesions but no change in ocular lesions).

[162]Vedat Hamuryudan et al., Thalidomide in the Treatment of the Mucocutaneous Lesions of the Behçet Syndrome, 128 Annals Internal Med. 443, 449 (1998).

recurred after thalidomide treatment ceased.[163]A disturbing and unique side effect was an increase in the number of ENL lesions during the first eight weeks of the thalidomide treatment.[164]

F. Side Effects

Despite the great strides made with thalidomide, researchers have been unable to prevent the dangerous side effects responsible for its notoriety. Aside from the drug's teratogenicity,[165]nerve damage, or neuropathy, remains the leading concern of widespread thalidomide use. Since the drug has been tested in such a wide range of diseases, the overall incidence of the condition is difficult to determine. While one retrospective study found thalidomide-induced neuropathy to occur in 21-50% of various dermatologic cases, others focus on specific disorders, citing rates as high as 70%.[166]Early reports that neuropathy does not strike ENL patients taking thalidomide (or occurs in as little as 1% of patients) have recently come into question by those who argue that the distinction between nerve damage caused by the leprosy itself and that caused by thalidomide was not properly made.[167]Furthermore, the use of thalidomide for complications of AIDS has presented special problems since preexisting neuropathy is common in HIV patients and such patients as a whole have been shown to be particularly sensitive to the drug.[168] While many studies report that the neuropathic symptoms (which include numbness of the arms, hands, legs, or feet as well as general

[163]See id.

[164]See id.

[165]Mortality after a mother's ingestion of thalidomide, either at birth or shortly thereafter, is reported to be approximately 40%. See FDA, Final Approval Labeling Text, 2 (visited March 26, 1999) <http://www.fda.gov/cder/news/ thalinfo/thalidomide.htm> [hereinafter Labeling Text].

[166]See Tseng et al, supra note 146, at 975-76.

[167]See id. at 975; Meyerson, supra note 102, at 390.

[168]See Perla Calderon et al., Thalidomide in dermatology. New indications for an old drug, 36 Int'l J. Dermatology 881, 884 (1997); Tseng et al., supra note 146, at 976.

muscle weakness) ceased upon discontinuation of the drug,[169]it is well known that thalidomide-induced nerve damage can be irreversible and can occur when even small doses of the drug are administered.[170] Aside from neuropathy and birth defects, thalidomide patients have reported, among other things, drowsiness, dizziness, mood swings, nausea, and headaches.

In sum, forty years of research have proven that the reviled drug of the 1950s and 60s can be used to treat life-threatening illnesses like cancer, complications from AIDS, and tuberculosis, but with the high likelihood of severe side effects. Due to specific modes of action, thalidomide has proven effective in some of the most difficult mycobacterial, autoimmune, and angiogenetic challenges facing the medical community today.

III. Approving Thalidomide

Amidst reports of both thalidomide's efficacy and the burgeoning black market of Brazilian thalidomide imports, FDA in 1995 solicited applications from manufacturers to market the drug.[171]Within a year, the Celgene Corporation, in its first-ever effort to bring a drug to the market, presented the government agency with its New Drug Application for Thalomid^{TM} (thalidomide), which would be used in the treatment of

[169]See e.g., Georgia B. Vogelsang, Letter to the Editor on Thalidomide Neuropathy, 327 New Eng. J. Med. 735 (1992) (stating that symptoms of neurotoxicity are rapidly reversible if thalidomide treatment ceases when symptoms first arise).

[170]See e.g., R.J. Stevens, The place of thalidomide in the treatment of inflammatory disease, 5 Lupus 257, 257 (1996) (discussing study's results of neuropathy after dose of 3g); Tseng et al., supra note 146, at 976.

[171]See Sheryl Gay Stolberg, Thalidomide Approved to Treat Leprosy, With Other Uses Seen, N.Y. Times, July 17, 1998, at A1. Until recently, thalidomide was available in Brazil without a prescription. See Cori Vanchieri, Preparing for Thalidomide's Comeback, 127 Annals of Internal Medicine 951, 952 (1997). Thalidomide was imported from Brazil and sold over the Internet. See Sheryl Gay Stolberg, Thalidomide Approved to Treat Leprosy, With Other Uses Seen, N.Y. Times, July 17, 1998, at A1.

the leprosy complication known as ENL.[172]Throughout the approval process FDA weighed the promising results against the chilling side effects, the possibility of treating life-threatening diseases against the rights of future children born with debilitating deformities, the availability and efficacy of alternative treatments, and the feasibility of instituting a restricted drug monitoring program.

On September 5, 1997, FDA's ten-person Dermatologic and Dental Drugs Advisory Committee recommended approval of the drug by voting 8-1 (with 1 abstention) that the benefits of Thalomid^{TM} outweighed the risks in the treatment of ENL.[173]FDA accepted the committee's endorsement and alerted the manufacturer that the drug would be approved once Celgene submitted plans for a satisfactory distribution system and agreeable labeling.[174]Over the next few months, Celgene worked with FDA, the Centers for Disease Control and Prevention, the Canadian Thalidomide Victims Association and numerous professional health organizations to craft the most restrictive distribution and monitoring program in the history of FDA.[175]With the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.^{TM}) Program in place, on July 16, 1998, FDA approved Thalomid^{TM} for ENL.[176] The S.T.E.P.S.^{TM} Program consists of five general components: 1) Registration of patients, participating physicians and pharmacies; 2) Required pregnancy testing before

[172]See Approval Letter, supra note 4.

[173]See generally, FDA Approves Thalidomide For Hansen's Disease Side Effect, Imposes Unprecedented Restrictions on Distribution, FDA Talk Paper T98-44 (July 16, 1998) (visited March 26, 1999) <http://www.fda.gov/bbs/topics/ANSWERS/ANS00887.html> [hereinafter FDA Approves Thalidomide]; Celgene Corp., Thalidomide Recommended for FDA Approval by U.S. FDA Advisory Committee (visited March 26, 1999) <http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=celg&script=410&layout=7&item_id=3032>.

[174]See FDA Issues Approvable Letter to Celgene For Thalidomide, FDA Talk Paper T97-44 (Sept. 22, 1997) (visited March 26, 1999) <http://www.fda.gov/bbs/topics/ANSWERS/ANS00820.html>; see also Celgene Corp., Celgene Corp. Receives FDA Approval Letter for Thalidomide First-Line Treatment for Complications of Leprosy (visited March 26, 1999) <http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=celg&script=410&layout=7&item_id=3033>.

[175]See Stuart L. Nightingale, From the Food and Drug Administration, 280 J. Am. Med. Ass'n 872, 872 (1998).

[176]See FDA Approves Thalidomide, supra note 173. It should be noted that FDA does not approve of the use of thalidomide alone in ENL patients suffering from varying degrees of neuritis. See Approval Letter, supra note 4.

and throughout thalidomide treatment; 3) Counseling in effective contraception; 4) Comprehensive physician, pharmacist, and patient education; and 5) Patient informed consent.[177] Thalomid^{TM} may only be administered by pharmacies and physicians who participate in the mandatory registration system, a nationwide program operated by Boston University School of Medicine's Slone Epidemiology Unit.[178]To register, a pharmacy must agree to comply with the S.T.E.P.S.^{TM} requirements: to confirm that the prescribing physician is in fact registered with Slone, verify the legitimacy of the patient's informed consent form, record the prescription information, and fill no more than a four-week dosage of the drug.[179]Automatic refills are expressly prohibited by the Program and the new prescription must have been written within the previous fourteen days.[180]Finally, pharmacists are not permitted to repackage the drug.[181] Similarly, a physician seeking to prescribe Thalomid^{TM} must register and agree to educate the patient about the dangers of the drug, provide contraceptive counseling, comply with the informed consent form requirements, and conduct acceptable pregnancy tests prior to and throughout the thalidomide treatment.[182] To be eligible for such treatment, a patient first must be capable of carrying out instructions and complying with the requirements of mandatory contraception, pregnancy testing, registration, and surveying.[183]Second, the patient must acknowledge in writing that he or she has received counseling on contraception and fetal defects and assert that he or she will comply with the contraceptive guidelines.[184]Third, if the patient is a minor, a parent or legal

[177]See Thalidomide approval brings tight restrictions on access, 55 Am. J. Health-Sys. Pharmacy 1746, 1746 (1998).

[178]See Nightingale, supra note 175, at 872.

[179]See Celgene Corp., System for Thalidomide Education and Prescribing Safety, (visited March 26, 1999) <http://www/celgene.com/STEPS.htm> [hereinafter Celgene STEPS].

[180]See FDA, Final Approval Labeling Text, 19 (visited March 26, 1999) <http://www.fda.gov/cder/news/thalinfo/thalidomide.htm> [hereinafter Labeling Text].

[181]See id.

[182]See Celgene STEPS, supra note 179.

[183]See Labeling Text, supra note 180, at 3.

[184]See id.

guardian must read and comply with the patient requirements.[185] Because Thalomid^{TM} is contraindicated in women of childbearing potential, the S.T.E.P.S.^{TM} Program's primary goal is to admit only those unable to become pregnant while on the drug. To this end, the Program requires proof of a negative pregnancy test conducted within the twenty-four hours before starting therapy.[186]Once therapy commences, additional pregnancy tests are to be conducted every week during the first month of Thalomid^{TM} intake and then every month in women with regular menstrual cycles (or bi-monthly in women with irregular cycles).[187]If a woman taking Thalomid^{TM} becomes pregnant, the therapy must end immediately and evaluation and counseling by a toxicology specialist is recommended.[188] Patients of both genders must receive contraception counseling. Female patients are required either to abstain from sexual intercourse or to utilize two forms of reliable birth control for one month prior to, throughout, and one month after thalidomide therapy.[189]The only patients exempted from this requirement are those who are infertile for reasons of menopause (for two years or longer) or hysterectomy; a general history of infertility is insufficient.[190]If a female patient decides to have sexual intercourse, her contraceptives must include at least one "highly effective method" (such as an IUD, birth control pill, tubal ligation, or partner's vasectomy) and one "effective method" (a latex condom, diaphragm, or cervical cap).[191]Because it is currently unknown whether thalidomide is present in ejaculate, male patients must agree to use a latex condom when engaging in sexual intercourse with a woman of childbearing

[185]See id.

[186]See id. at 9.

[187]See id.

[188]See id.

[189]See id. at 8-9.

[190]See id. at 2.

[191]See id. at 9.

potential, even if the patient has had a successful vasectomy.[192] The fourth component of the S.T.E.P.S.™ Program requires all participating parties to be educated on the dangers of thalidomide. For example, health care professionals receive the twenty-two page package insert that outlines, among other things, the physician and pharmacist requirements, clinical study results, precautions, and adverse effects.[193]Patients are required to receive a videotape featuring a member of the Canadian Thalidomide Victim Association, a brochure with pictures of thalidomide-affected babies, and a letter detailing the likely effects on the fetus of a pregnant woman taking thalidomide.[194] Lastly, S.T.E.P.S.™ requires a patient's informed consent. The agreement's text must be read aloud to the patient, in the language of his or her choice, and the patient must initial each of the statements on the gender-specific form.[195]Both male and female forms require the patient to participate in the national registry and to agree never to share the drug with others.[196]In addition, both men and women must verify that the prescribing physician has answered all of their questions and that they have viewed the videotape or read the brochure included in the patient educational packet.[197] After this, the two forms differ in their emphases on sex-specific risks. The female form, for example, goes on to specify the requirements of the pregnancy test regime, the forms of acceptable birth control, and the actions to take if a patient misses her menstrual period.[198]In addition, a consenting female must pledge not to try to become pregnant and must agree that "I have been warned by my doctor that my unborn baby will almost certainly have serious birth defects or may even die if I am pregnant or become pregnant while taking

[192]See id. at 4, 6.

[193]See id., passim.

[194]See Nightingale, supra note 175, at 872.

[195]See Labeling Text, supra note 180, at 21.

[196]See id. at 20-21.

[197]See id.

[198]See id. at 20.

THALOMID^{TM} (thalidomide)."[199]Conversely, the male form focuses on the dangers of unprotected sexual intercourse with a woman.[200] In addition to the five components of S.T.E.P.S.^{TM}, the program also requires that Celgene notify FDA within fifteen days of receiving a report that a fetal exposure to thalidomide has occurred.[201]Upon the report of a single case, FDA has stated it will reevaluate the entire Program and consider withdrawing the drug's approval.[202] The demand for Thalomid^{TM} is greater than was anticipated. The 1998 figures indicate that the drug's gross sales were over $3.5 million[203]and while only 2000 physicians and 2000 pharmacists were originally expected to participate in the S.T.E.P.S.^{TM} Program in the first year of marketing,[204]the numbers are currently at 4000 and 6000, respectively.[205]It is estimated that at least 6000 patients are enrolled in the Program.[206] While the S.T.E.P.S.^{TM} Program has been lauded as the greatest balance between individual and fetal rights, it isn't without its problems. The approval of this teratogenic drug inevitably will result in the births of babies with severe defects; as the medical community is fond of saying, there is no such thing as zero risk. At its base, then, the Program was created not as cure to the

[199]Id.

[200]See id. at 21.

[201]See id. at 2; Approval Letter, supra note 4.

[202]See Thalidomide approval brings tight restrictions on access, 55 Am. J. Health-Sys. Pharmacy 1746, 1749 (1998). It is also important to note that a change in the S.T.E.P.S.^{TM} Program without prior approval from the FDA may result in a finding that Thalomid^{TM} is misbranded and unapproved. See Approval Letter, supra note 4.

[203]See Celgene Corp., Celgene Corp. Announces Fourth Quarter Results and Growing Sales of Thalidomide (visited March 26, 1999) <http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=celg&script=410&layout=7&item_id=20606>.

[204]See The problem with thalidomide's new incarnation, 16 Nature Biotechnology 695, 695 (1998).

[205]Telephone Interview with Dr. Ken Restak, Medical Information Officer, Celgene Corp. (March 19, 1999).

[206]See id. Although Dr. Restak would not divulge the number of patients currently enrolled in the S.T.E.P.S.^{TM} Program, he did note that it was fair to assume one patient for each of the 6000 pharmacies enrolled. See id. Although it is entirely conceivable that more than 4000 patients will be added in the next four months, Restak's calculations comport with the July 1998 statement of Bruce Williams, the marketing director of Celgene, estimating that fewer than 10,000 patients would use Thalomid^{TM} in the first year. See Stolberg, supra note 171, at A1.

thalidomide problem but as a prophylactic measure meant to prevent as many birth defects as possible. The next part of this paper discusses the inherent loopholes of the S.T.E.P.S.^{TM} Program.

For one, patients simply might not comply with the Program requirements. One area in which FDA has no control is the continuous abstinence exception to the two-contraception rule. To qualify for this exemption, female patients need only state their intention to abstain from sexual intercourse throughout their treatment and for one month following discontinuance of the drug. A sexually active woman experiencing general infertility problems (not due to hysterectomy or menopause) may not want to trouble herself with the contraception requirements and therefore may declare a false promise to abstain, honestly believing that she will never become pregnant. Her continued sexual activity without contraceptives could result in a thalidomide-affected pregnancy.

Just as likely, patients may not adhere to the contraceptive plan. If a female patient's "highly effective" method choice is hormonal, deviation from the instructions (for example, forgetting to take a birth control pill or choosing not to take the pills at the same time every day) and failure of the "effective method" (for instance, a tear in a latex condom or improper positioning of a diaphragm) could result in pregnancy. Likewise, a male patient may not use a latex condom in every instance of sexual intercourse with a woman of child-bearing potential and fertilization may result.

A final and serious deviation from the Program requirements involves drug sharing. Although explicitly instructed not to give the drug to others, including those who experience the patient's same symptoms, patients may nevertheless do so. The threat of exposing an unborn child to thalidomide greatly increases with drug sharing since the second recipient has not been instructed in any of the risks thus negating any possibility of informed consent.

A second broad issue is that the Program operates in an environment where off-label uses are the norm. When prescribing drugs, physicians are not limited by the drug's specifically approved purpose; rather, FDA

policy states that physicians are free to prescribe a drug for the treatment of any disease.[207]For instance, a participating doctor may prescribe Thalomid^{TM} for cachexia and breast cancer as well as for the approved ENL use. One commentator believes that the availability of off-label usage will make thalidomide one of the most prescribed drugs of the 21st century.[208] This physician discretion could be extremely detrimental to the health of the patient. Implicit in any drug's approval is a finding by FDA that the drug is safe and effective for it's stated purpose. Once the physician ventures into unproven territory by deviating from the drug's labeled use, she is in effect conducting her own investigational research. While it could be argued that modern medicine is dependent upon this case-by-case experimentation, it is clear that all physicians should not be engaging in such conduct. Misinformed or poorly trained physicians could cause more harm than good. In the case of thalidomide, for example, a prescribing physician would more likely than not educate himself as part of the S.T.E.P.S.^{TM} requirement for registration, but if he were inadequately trained in electrophysiological measuring or other methods of testing for peripheral neuropathy, his patient may suffer irreversible nerve damage. Similarly, a physician may decide to prescribe thalidomide in the hopes of treating the newly-studied Kaposi's sarcoma and instead increase the HIV-viral load, putting the patient in greater danger of succumbing to the disease.

The problem of physician discretion is exacerbated by pressure from uninformed patients. Results of an FDA study show that two-thirds of those surveyed under the age of forty-five could not define the word "thalidomide."[209]Without the perspective of history, young people may learn of thalidomide's positive results, demand it from their physicians, and undaunted by their first refusal, go in search of a physician who

[207]See e.g., Legal Status of Approved Labeling For Prescription Drugs; Prescribing For Uses Unapproved By The Food and Drug Administration: Notice of Proposed Rule Making, 37 Fed. Reg. 16503 (1972) (proposed Aug. 15, 1972) (stating that a physician may lawfully vary the use from those included in the package insert).

[208]See Jennifer A. Galloway, Drug's Rediscovery Brings Dose of Danger Thalidomide Requires Birth-Defect Warning, UW Ethicist Says, Wis. St. J., Aug. 7, 1998, available in 1998 WL 14527257.

[209]See Charles Marwick, Thalidomide Back---Under Strict Control, 278 J. Am. Medical Ass'n 1135, 1135 (1997).

will prescribe it to them. By way of comparison, Dr. Gail J. Povar, of the George Washington University School of Medicine, has said that "[e]very week I have a teenager ask for Accutane inappropriately. We have to accept the fact that this will happen with thalidomide and be prepared."[210] Finally, while the tensions of the S.T.E.P.S.™ Program discussed above focus on the leniency of certain provisions, an argument can be made that the strictness of the Program as a whole will drive some Americans to secure access to thalidomide through other, illegal channels and therefore increase the risk to unborn children. While suppressing the unlawful distribution of thalidomide was originally one incentive for FDA to approve the drug, the decision itself did not automatically shut down the preexisting black market. The increased availability due to approval in this country combined with the already developed markets in approximately thirty-nine other countries[211]makes it more likely that thalidomide will be obtainable outside of the S.T.E.P.S.™ Program. Supporting this proposition is an example from a 1993 British documentary, *Thalidomide: the drug that came back*, which focused on the state of the Brazilian leprosy program.[212]Despite government officials' assertions that the drug was not available to women of childbearing age and could only be distributed from government-controlled facilities, the documentary producers were able to catch on hidden camera a pharmacy dispensing thalidomide to a young woman.[213] It also has been suggested that developing counties will take their cue from the United States' approval of thalidomide and will begin issuing the drug without implementing a restricted distribution plan similar to S.T.E.P.S.™.[214]Scholars have noted that in countries

[210]See Vanchieri, supra note 171, at 952. Dr. Povar also noted, ''What worries me is that there may be desperate patients who will try to go beyond the well-documented indications to more experimental applications.'' See Marwick, supra note 203, at 1136.

[211]Thalidomide is available in eight of ten South American countries. See Vanchieri, supra note 171, at 952. In 1994, 39 countries used thalidomide for the treatment of lepra reaction. See James Cutler, Thalidomide revisited, 343 Lancet 795, 795 (1994).

[212]See Cutler, supra note 211, at 795.

[213]See id. at 796; see also P.F. D'Arcy et al., Thalidomide revisited, 13 Adverse Drug Reactions and Toxicology Rev. 65, 73 (1994).

[214]See Vanchieri, supra note 171, at 952.

like Brazil, where there is a high percentage of leprosy and where Catholicism is the predominant religion, women of child-bearing age will not adhere to the contraception requirements so as not to contradict a central teaching of their faith and will bear children with severe birth defects.[215]

As evidenced by the above, there are strong indications that human behavior is mainly responsible for failings of the S.T.E.P.S.™ Program. The regime is not error-free but, as will be argued in the following two sections, the Program contains the best set of requirements for protecting both a possible fetus and a woman's right to choose treatment.

IV. Precedent for the FDA Decision

While shocking to an American public who remember the pictures of the thalidomide babies of the 1950s and 1960s, the decision to approve the drug, or in stark terms the subordination of protecting a possible fetus to individual choice, is supported by events of FDA recent history. For one, FDA policy in the clinical trial context has evolved from a position of overprotecting fetal rights to one where a delicate balance is struck in favor of the informed woman. As will be described below, the agency shifted from what was, for all intents and purposes, a ban on all women of childbearing potential from clinical trials to a position of strong encouragement for the inclusion of such subjects. Second, FDA approved the known teratogen isotretinoin, or Accutane, and despite continuing reports of numerous drug-induced birth defects, the drug remains on the market. Combined, these two examples provide a background for the approval of thalidomide and support the striking of the balance in favor of informed, individual choice.

The debate over gender in clinical trials has been very active in recent years. Due to efficiency-minded drug manufacturers and a fetal-protective FDA, the white male historically occupied the clinical trial field,

[215] See D'Arcy et al., supra note 213, at 73.

foreclosing women's opportunities for the advanced techniques, better care, and psychological optimism that accompany trial participation. Over the years, however, the shortcomings of this regime have become apparent and FDA has reoriented it's position. Demonstrating its new policy choice of an individual's informed consent over possible or even actual fetal rights, FDA now encourages researchers to include women, even some pregnant women, in clinical trials.[216] Women were traditionally excluded from clinical trials for a myriad of reasons. For one, menstruation, pregnancy, and menopause worked against the homogeneity drug manufacturers sought in test subjects.[217]Second, accounting for the additional complexities women added to the calculus would be expensive.[218]Third, the manufacturers feared the liability that would attach if a female test subject became pregnant and gave birth to a child with drug-induced defects.[219] Early FDA policy on female inclusion, designed in the wake of the thalidomide tragedy, eased these manufacturer concerns. Under the agency's 1977 Guideline, entitled "General Considerations for the Clinical Evaluation of Drugs," researchers were able to continue their male-dominated research. The Guideline stated in part:

> *In general, women of childbearing potential should be excluded from the earliest dose ranging studies.* If adequate information on efficacy and relative safety has been amassed during Phase II, women of childbearing potential may be included in further studies provided Segment II and the female part of Segment I of the FDA Animal Reproduction Guidelines have been completed. All three segments should be completed before large-scale clinical trials are initiated in women of childbearing potential.[220]

The 1977 Guideline went on to define a woman of childbearing potential as a "premenopausal female capable of becoming pregnant."[221]This included women using oral, injectable, and mechanical forms of birth control,

[216]See infra notes 227-242 and accompanying text.

[217]See L. Elizabeth Bowles, The Disenfranchisement of Fertile Women in Clinical Trials: The Legal Ramifications of and Solutions for Rectifying the Knowledge Gap, 45 Vand. L. Rev. 877, 881 (1992).

[218]See id. at 882.

[219]See id. at 880.

[221]Id. at 1237 n. 244.

lesbians, and married women whose husbands had been vasectomized.[222]In an effort to "protect" women, FDA was doing more harm than good: the government agency was approving drugs for women based on proof of efficacy and safety from male-only trials.[223] Although narrow exceptions to the ban on women in clinical trials did exist,[224]manufacturers interpreted the 1977 Guideline as requiring the exclusion of women.[225]Inevitably, this led to a slower understanding of female reactions to drugs and, in essence, fewer advances in women's health. After an audit by the General Accounting Office concluded the obvious that the 1977 Guideline contributed to the underrepresentation of women in drug trials,[226]FDA in 1993 promulgated the "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs."[227]The Supplementary Information to the 1993 Guideline states in part:

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[222]See id.

[223]See e.g., Rothenberg, supra note 220, at 1238-39 (noting that the 1977 Guidelines allowed FDA to approve a drug without the manufacturer ever testing it on a woman).

[224]See id. at 1237 (stating that women of childbearing potential could be admitted to a clinical trial if (1) the purpose of the drug was to save or prolong life; (2) the drug belonged to a class of compounds for which teratogenic potential had already been established in animals; and (3) institutionalization of the woman had allowed investigators to verify that she was not pregnant).

[225]See Vanessa Merton, The Exclusion of Pregnant, Pregnable, and Once-Pregnable People (A.K.A. Women) From Biomedical Research, 3 Tex. K. Women & L. 307, 337 (1994).

[226]See Rothenberg, supra note 220, at 1239.

[227]58 Fed. Reg. 39,406 (1993) (proposed July 22, 1993).

> The agency has reconsidered the 1977 guideline and has concluded that it should be revised. This does not reflect a lack of concern for potential fetal exposure or indifference to potential fetal damage, but rather the agency's opinion that (1) exclusion of women from early trials is not medically necessary because the risk to fetal exposure can be minimized by patient behavior and laboratory testing, and (2) initial determinations about whether that risk is adequately addressed are properly left to patients, physicians, local IRB's, and sponsors, with appropriate review and guidance by FDA, as are all other aspects of the safety of proposed investigations. *The agency is, therefore, withdrawing the restriction on the participation of women of childbearing potential in early clinical trials....*[228]

Because FDA never codified the 1993 standard as a regulation, the Guideline remains a policy statement without the force of law. Academic disagreement focuses not on the deference to be afforded the promulgation but on its importance. For some scholars, the 1993 Guideline is seen as the product of a weak FDA who, in an attempt both to appease women in their demand for equal access to clinical trials and pacify the manufacturing powerhouses, protected itself with unenforceable and meaningless precatory language.[229]However, the better view is one that sees the Guideline as a positive move toward equality.[230] At the heart of the 1993 promulgation lies the explicit elimination of the 1977 Guideline's prohibition of women of childbearing potential in early stages of clinical trials.[231]The agency baldly admits that its 1977 Guideline not only perpetuated the male subject paradigm, but was responsible for the medical community's lag in understanding gendered reactions to different drugs.[232]FDA dedicates an entire section of the 1993 Guideline to discussing

[229]See e.g., Merton, supra note 225, at 338 (describing the 1993 Guideline as a ''pretty please' to the pharmaceutical houses, with a gratuitous abandonment of regulatory authority that is both unwarranted as a matter of law and not too smart as a matter of strategy''); see also Rothenberg, supra note 220, at 1240-41 (critiquing the 1993 Guideline). For example, the second sentence of the text denies any force the Guideline is perceived to have when it states that it ''does not bind the agency, and it does not create or confer any rights, privileges, or benefits for or on any person.'' 58 Fed. Reg. 39,406, 39,409 (1993) (proposed July 22, 1993). The Guideline merely encourages the inclusion of women in Phases I and II of clinical trials and while ''[a]nalyses to detect the influence of gender should be carried out,'' they are not required. Id. at 39,410. Finally, instead of regulating such inclusion, FDA asserts that it ''is confident that the interplay of ethical, social, medical, legal and political forces will allow greater participation of women in the early stages of clinical trials.'' Id. at 39,408-409.

[230]R. Alta Charo, Protecting Us To Death: Women, Pregnancy, and Clinical Research Trials, 38 St. Louis U. L. J. 135, 137 (1993).

[231]See 58 Fed. Reg., at 39,410 (''Note that the strict limitation on the participation of women of childbearing potential in phase 1 and early phase 2 trials that was imposed by the 1977 guideline... has been eliminated.'').

[232]See id. at 39,408.

the inclusion of both genders in clinical studies, stating that studies should "reflect the population that will receive the drug when it is marketed" and therefore, "representatives of both genders should be included in... numbers adequate to allow detection of clinically significant gender-related differences in drug response."[233] Despite the shift in policy, the 1993 Guideline continues to protect the fetus by outlining the measures to be taken to minimize "inadvertent exposure of fetuses to potentially toxic agents...."[234]The manufacturer is required to obtain informed consent and is permitted to require pregnancy testing and abstinence or contraception protocols.[235] In the end, however, the 1993 Guideline represents a striking of the balance in favor of informed consent. As one scholar notes, it is "an acknowledgment that women, even if they are fertile, are competent to give informed consent to their participation in research trials, and that this informed consent provides the necessary insulation to protect researcher and manufacturer from suit by mother or possible child for all but negligent enrollment practices."[236] This shift in policy was confirmed when, in 1997, FDA proposed a new regulation involving the use of clinical holds.[237]According to the proposal, FDA could place a clinical hold on a study upon a finding that men or women of childbearing potential with life-threatening diseases were being excluded because of a researcher's perceived risk that reproductive or developmental harm would result.[238]While the proposed rule encompasses both genders, "the primary goal of this proposed

[233]Id. at 39,410.

[234]Id. at 39,411.

[235]See id.

[236]Charo, supra note 230, at 158.

[237]21 C.F.R.312.42 states in part:

> A clinical hold is an order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation.... When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; patients already in the study should be taken off therapy unless specifically permitted by FDA in the interest of patient safety. Id.

[238]See 62 Fed. Reg. 49,946, 49,951 (1997) (proposed Sept. 24, 1997); Anna C. Mastroianni, HIV, Women, and Access to Clinical Trials: Tort Liability and Lessons from DES, 5 Duke J. Gender L. & Pol'y 167, 171 n.13 (1998).

amendment is to ensure that women with reproductive potential who have a life-threatening disease are not automatically excluded in the future...."[239]In support of the policy, FDA argues that the ethical principle of justice requires that "the burdens and benefits of participation in clinical research be equitably distributed across the entire population in the place or region where the clinical research is conducted."[240] Today, even pregnant women are included in clinical trials. Admittedly, the 1997 policy shied away from advocating for their blanket inclusion, but researchers can no longer ignore the societal benefits of doing so.[241]For example, in admitting pregnant women to clinical trials of AZT, researchers have confirmed the reduction in maternal-fetal transmission of HIV when the drug is administered to the mother during pregnancy and to the infant for six weeks following birth.[242] From the overprotection of the fetus to deference given to the choice of a woman who has been educated on all of the risks, the evolution in FDA policy provides overwhelming support for the agency's approval of thalidomide. In a sense, the thalidomide policy debate had already been acted out under the hot lights of the clinical trial stage. The desire to protect potential unborn children. The possibly life-saving benefits to admitted women. The importance of informed consent. And in the end, the decision not only to allow a woman to make her own reproductive choices but to permit her access to a possibly life-saving drug.

These and similar policy debates also took place over the drug isotretinoin, another teratogenic drug that greatly influenced the approval of thalidomide. The drug, more commonly called by its generic name Accutane, was first developed in Europe in the 1950s but never marketed because of the protest the teratogen was

[239]See 62 Fed. Reg. 49,946, 49,946 (1997).

[240]Id. at 49,949.

[241]The policy states that ''FDA does not intend the phrase 'women with reproductive potential' to include pregnant women.'' 62 Fed. Reg. 49,946, 49,947 (1997).

[242]See Mastroianni, supra note 238, at 170, 183; see also Cynthia Mederios, The Eligibility of Women for Clinical Research Trials, 13 J. Clinical Oncology 293, 296-97 (1995) (W. Bradford Patterson & Ezekiel J. Emanuel eds.) (describing ACTG protocol no. 076 results of 67% reduction in maternal-fetal HIV transmission).

certain to meet in the wake of the thalidomide devastation.[243]It is somewhat surprising then that in 1982, FDA approved the Roche Pharmaceuticals drug application for the treatment of severe recalcitrant cystic acne, an unsightly disease resulting in deep scars on the face, neck, back, chest, and groin.[244]Because of the drug's early test results, Accutane's original labeling included information about birth defects in animals but was silent about any human consequences.

The proliferation of off-label usage soon made Accutane the drug of choice for treating all types of acne. Heralded as a medical breakthrough, as many as 90% of dermatologists prescribed the drug in its first year on the market.[245]It was later reported that in its first five years, only 53,000 women between the ages of fifteen and forty-four had cystic acne but that between 270,000 - 390,000 women had actually received the drug.[246] Reports of the first Accutane-induced birth defects arrived at FDA within the first year of the drug's approval. With what would later be termed "isotretinoin syndrome," babies were born with a combination of heart and central nervous system problems, malformed or absent ears, wide-set eyes, a smaller mouth and jaw, and sometimes a cleft palate.[247]The company responded with a series of labeling changes, "Dear Doctor" letters, and even a warning campaign featuring a "Medical Director's Page" in industry journals, yet the number of Accutane babies continued to rise.[248] In February 1988, a division of FDA, the Office of Epidemiology and Biostatistics, recommended that Accutane be withdrawn from the market.[249]Another re-

[243]See Diane Acker Nygaard, Accutane: Is the Drug a Prescription for Birth Defects?, Trial Dec. 1988, at 89.

[244]See generally FDA, Isotretinoin (Accutane) Birth Defects 1 (visited March 26, 1999) <http://www.fda.gov/bbs/topics/ANSWERS/ANS00251.html> [hereinafter FDA Isotretinoin Statement].

[245]See Janice S. Lewis, Accutane and Birth Defects, Trial April 1985, at 16.

[246]See Claudia J. Postell, Popular Anti-Acne Drug Linked to Birth Defects, Trial, June 1988, at 89.

[247]See Lewis, supra note 245, at 16; Nygaard, supra note 243, at 90.

[248]See Lewis, supra note 245, at 17.

[249]See Nygaard, supra note 243, at 89.

port in April of that year opined that the warnings and campaigns undertaken by Roche had failed.[250]While only sixty-two cases of Accutane-related birth defects had been reported to FDA by the early months of 1988,[251]the agency estimated that the total number of affected births was between 900 and 1,300.[252]The agency also believed that the drug had caused 700 to 1,000 spontaneous abortions while another 5,500 to 12,500 women had terminated their pregnancies because of a fear of birth defects.[253]It was discovered that a woman exposed to Accutane in her first trimester of pregnancy has a 40% chance of miscarriage and a 25% chance of delivering a malformed child.[254] In April 1988, FDA's Dermatologic Drugs Advisory Committee convened to consider, among other things, the recommendation by the Office of Epidemiology and Biostatistics to withdraw agency approval of the drug.[255]The seven-member panel, many members of which were self-interested dermatologists, not surprisingly rejected the proposal but, in a bold move, proposed a novel program of limited distribution (an approach only seen in Europe), education, and written informed consent.[256]In the end, FDA adopted neither the Committee's limited distribution proposal nor the Epidemiology recommendation for withdrawal. Instead, the agency built upon the Committee's recommendations and required the manufacturer to adhere to a strict new set of standards. Roche incorporated these standards into the plan that would later serve as the model for Thalomid's™ S.T.E.P.S.™ Program.

In late 1988, Roche unveiled the unprecedented Pregnancy Prevention Program for Women on Accutane (PPP).[257]First, the PPP includes a substantial patient and physician education package. The materials

[250]See id. at 90.

[251]See FDA Isotretinoin Statement, supra note 244, at 2.

[252]See Nygaard, supra note 243, at 90.

[253]See Postell, supra note 246, at 89.

[254]See Nygaard, supra note 243, at 89, 90.

[255]See FDA Isotretinoin Statement, supra note 244, at 3.

[256]See Nygaard, supra note 243, at 90.

[257]See FDA, Accutane Update, FDA Talk Paper T90-25, 1 (May 22, 1990). Amendments to the Program

include brochures that outline the likelihood of birth defects and methods of effective birth control, a patient qualification checklist which should be completed before beginning Accutane therapy, consent forms and supplementary guides on informed consent, and information on a toll-free telephone number set up to offer Accutane information in thirteen different languages.[258]The physician is warned of fetal abnormalities associated with Accutane and is instructed on the prescribing requirements.[259] Second, the PPP constructs a series of hurdles designed to prevent pregnancy. For example, a patient must have a negative pregnancy test within seven days of beginning Accutane therapy and may only begin such therapy on the second or third day of her next menstrual cycle.[260]After receiving contraception counseling (from the prescribing physician or from a manufacturer-paid contraception specialist), the patient must agree either to abstain from sexual intercourse or to use two forms of effective birth control for one month before, throughout, and one month after drug therapy.[261]The container itself also warns of fetal risks; the drug can only be administered in its special 10-capsule blister package that contains drawings of disfigured children and the "Avoid Pregnancy" symbol (consisting of a line through a picture of a pregnant woman).[262] The third component of the PPP is the voluntary registry operated by the same group overseeing S.T.E.P.S.^{TM}, the Slone Epidemiology Unit at

were made in 1990. See Dr. Allen A. Mitchell, Remarks at Thalidomide: Potential Benefits and Risks, An Open Public Scientific Workshop (Sept. 9, 1997) (transcript available at page 124 of <http://www.fda.gov/oashi/patrep/nih99.html#mitch> (visited March 26, 1999)) [hereinafter Mitchell Remarks].

[258]See Mitchell Remarks, supra note 257, at 121-22.

[259]For example, a woman of childbearing potential should not receive the drug unless she 1) has severe recalcitrant cystic acne; 2) understands and is able to follow instructions; 3) has received oral and written warnings of the dangers of becoming pregnant while on Accutane, the need to abstain from sexual intercourse or to use two forms of birth control, and has provided her consent; 4) has had a negative pregnancy test within seven days before starting Accutane therapy; and 5) will begin the therapy on either the second or third day of her next menstrual cycle. See Roche Pharmaceuticals, Accutane Complete Product Information 2 (visited March 26, 1999)<http://www.rocheusa.com/products/accutane/
pi.html> [hereinafter Roche Information].

[260]See id.

[261]See id. at 2; Mitchell Remarks, supra note 257, at 121-22, 124; Gideon Koren et al., Drug Therapy, 338 New Eng. J. Med. 1128, 1130 (1998).

[262]See Mitchell Remarks, supra note 257, at 122; Rita Rubin, Thalidomide Could Guide Use of Drugs That Risk Birth Defects, USA Today, July 22, 1998, at 7D.

Boston University. As part of the 1988 instructions, FDA required the implementation of a study to evaluate patient compliance and Accutane-related pregnancies.[263]Patients in the Slone study are paid $10 to enroll and to participate in telephone interviews.[264] These interviews ferret out the information exchanged between doctor and patient, sexual activity, contraception compliance, and pregnancy, and are conducted at the beginning of therapy, the middle, and during a later "follow-up" period after therapy has ended.[265]More than 350,000 women, or approximately half of all Accutane patients, have enrolled in the voluntary program.[266] Since no program can ensure zero risk, it is not surprising that some women in the PPP did become pregnant. Data compiled between 1989 and 1995 show that of the 210,000 women who completed the final "follow-up" interview, 623 became pregnant.[267]Of those 623 pregnancies, almost two-thirds resulted from contraceptive failure, 27% from lack of contraceptive use, and 9% of the women were already pregnant when the Accutane therapy began.[268]The data also indicates that almost 90% of the pregnancies were aborted—roughly two-thirds electively and 16% spontaneously.[269]Birth defects were present in 25 - 30% of the live-birth cases.[270] Despite the fact that an average of six new Accutane births are reported to FDA every year, the drug remains on the market and sales continue to rise.[271]Thus, Accutane represents yet another marker in FDA's

[263]See Nygaard, supra note 243, at 90.

[264]See Mitchell Remarks, supra note 257, at 122
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[265]See id. at 123.

[266]See id.; Rita Rubin, supra note 262, at 7D. It has been suggested that the PPP results are skewed by the type of registry participant. Specifically, ''women who are sufficiently motivated to participate in a research study are also sufficiently motivated to avoid becoming pregnant while taking isotretinoin.'' James L. Mills, Protecting the Embryo from X-Rated Drugs 1 (visited March 26, 1999) <http://www.nejm.org/content/1995/0333/0002/0124.asp> (reprinted in 333 New Eng. J. Med. 124 (1995)).

[267]See Mitchell Remarks, supra note 257, at 125; Vanchieri, supra note 171, at 952; Jane L. Miller, Thalidomide recommended for approval under tight restrictions, 54 Am. J. Healt-Sys. Pharmacy 2270, 2277 (1997).

[268]See Mitchell Remarks, supra note 257, at 125.

[269]See id.

[270]See id.

[271]See Bob Van Voris, Will Liability Cloud Use of Thalidomide? Renewed Interest for a Spate of Diseases, But Risks Remain, Nat'l L. J., Sept. 22, 1997, at B1; Hoffman-La Roche, 1997 Annual Report (visited March 26, 1999)

evolution toward providing a woman care after she consents to the risks of that care to a possible fetus.

It has been suggested that characteristics specific to Accutane might distinguish it from thalidomide and therefore any comparison of the two drugs should be limited.[272]The first argument offered is that Accutane is available only from a single manufacturer which supports a strict pregnancy prevention program.[273]This, however, actually supports the approval of Thalomid ^{TM}. While admittedly there are illegal means of procuring the drug, thalidomide has only been approved for distribution by Celgene, a corporation dedicated to the S.T.E.P.S.^{TM} regime. The second argument is that 92% of women enrolled in the PPP received Accutane from dermatologists whereas Thalomid^{TM} is prescribed by a range of physicians for various diseases.[274]Certainly, a broad campaign could be as effective as the targeting of a specific field of medicine in educating the medical community on a drug's teratogenic risks. Furthermore, concentrating efforts on dermatologists alone increases the chance that other prescribing physicians will not be as apprised of the risks inherent in the drug. Third, the Accutane patient population has been called "well-educated" and of a "higher socioeconomic status" leaving the inference that they will more likely understand the risks of pregnancy while undergoing Accutane therapy.[275]As a general matter, who is to say that American cancer,

<http://www.roche.com/roche/finance/arep97/dp02.htm> (reporting that Accutane brought Roche's parent company a sum of over 500 million Swiss francs). Recently, it was reported to FDA that twelve patients, since 1989, had committed suicide while on Accutane. See Lynne Lamberg, Acne Drug Depression Warnings Highlight Need for Expert Care 1 (visited March 26, 1999) <http://www.ama-assn.org/sci-pubs/journals/archive/jama/vol_279/no_14/jmn80043.htm> (reprinted at 279 J. Am. Med. Ass'n 1057 (1998)). Roche added an addition warning on the drug's label, which reads: ''Psychiatric Disorders: Accutane may cause depression, psychosis, and, rarely, suicidal ideation, suicide attempts and suicide. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary. No mechanism of action has been established for these events.'' Roche Information, supra note 250, at 4.

[272]See Miller, supra note 267, at 2277. The author believes that Miller mistakenly interpreted the comments of Dr. Allen Mitchell, the associate director of the Slone Epidemiology Unit, during his speech at the thalidomide scientific workshop on Sept. 9, 1997. Indeed, Dr. Mitchell explained the special characteristics of Accutane that he believed must be taken into account when evaluating the effectiveness of the PPP. See Mitchell Remarks, supra note 257, at 126. However, the author does not believe that Dr. Mitchell meant to paint thalidomide's approval in an unfavorable light. Therefore, the accompanying text refutes Miller's inference.

[273]See Mitchell Remarks, supra note 257, at 126.

[274]See id.

[275]Id.

leprosy, and AIDS patients aren't just as likely to be educated and of a "higher socioeconomic status?"

There are, however, some legitimate distinctions between Accutane and thalidomide. For one, Accutane is proven to be the only effective treatment for some cases of severe, cystic acne. Contrariwise, many of the diseases for which thalidomide has been found to be effective have alternative treatments. Although these alternatives are not as efficacious and do not act as expediently, they do, nonetheless, exist. Another distinction arises in the duration of the two therapies. While cystic acne usually clears up after five months of Accutane treatment, it is common for thalidomide users to relapse upon withdrawal of the drug. It is possible that it is more difficult to comply with stringent anti-pregnancy programs for longer than for shorter periods of time, and thus more pregnancies would occur among thalidomide users than those on Accutane. On the whole, however, a comparison of thalidomide and Accutane reveals that the justifications for approving the former are actually much stronger than the latter. There are three major issues: (1) the health of the woman in each case; (2) the general age of the patient populations; and (3) the strictures of the S.T.E.P.S.^{TM} Program versus the PPP.

First, thalidomide is used to treat life-threatening illnesses while Accutane is prescribed for an inherently cosmetic condition. At its best, Accutane relieves the damaging psychological effects caused by an unattractive complexion, some of which are so powerful that a few sufferers have even attempted suicide.[276]Thalidomide, on the other hand, has the capacity to surpass cosmetic and psychological effects by saving lives and treating the epidemics of our time.

Second, the age differences in the patient populations of the two drugs may contribute to different degrees of compliance. Since acne is so common in teenagers, it is not surprising that the Accutane patient population is comprised of a high percentage of young people. However, these young adults are more likely than their

[276]See e.g., Lamberg, supra note 271, at 1,3 (''[p]sychological scarring is an important aspect of the illness, and it has not received enough attention.'').

older counterparts to engage in sexual activity without contraception thus making Accutane births more likely.[277]Confirming this hypothesis, one article states that "half the deformed children were born to teenage mothers."[278] The age-to-risk ratio is not as glaring in the case of thalidomide as there is no evidence that young adults constitute a high percentage of potential thalidomide patients.

Finally, the differing provisions and requirements of the two anti-pregnancy programs favor the approval of thalidomide. Although the PPP was used as a model for S.T.E.P.S.^{TM}, the latter program is better formulated to protect against pregnancy. Putting aside the similarities, the following table compares the differences between the two regimes:

[277]See e.g., Nygaard, supra note 243, at 91 (stating that teenagers have a high incidence of sexual activity and low incidence of contraceptive use).

[278]Id.

Table: Comparison of S.T.E.P.S.^{TM} and PPP Differences

System for Thalidomide Education and Prescribing Safety™	**Pregnancy Prevention Program for Women on Accutane**
Limited Distribution (only certain physicians and pharmacies can prescribe)	Unlimited Distribution
Pharmacists: only may fill a 28-day dosage and no automatic refills. New prescription, written in the previous 14 days, required each time	Pharmacists: No such requirements
Negative Pregnancy Test: within 24 hours of beginning therapy	Negative Pregnancy Test: within 7 days of beginning therapy
Further Pregnancy Tests: every week for first month; then monthly or bi-monthly, depending on regularity of menstrual cycle.	Further Pregnancy Tests: only recommended

Consent Form: • Lists methods of acceptable birth control • Videotape of thalidomide-affected person • Instructed not to share drug with others	Consent Form: • No such listings
Mandatory Registration with Slone	Voluntary Registration with Slone

In the end, both the clinical trial debate and Accutane approval provide ample support for FDA's decision to approve thalidomide. With regards to clinical trials, FDA has settled on a policy of including women once they have consented to the risks associated with such participation. Extending this policy to the drug context, the agency has weighed in on the side of an informed woman who consents to an Accutane therapy that might be harmful to a possible fetus if she fails to follow the consented-to requirements. As has been

shown, thalidomide approval is supported by these two examples and presents an even stronger case since the stringent requirements of the S.T.E.P.S.^{TM} Program provide even more protection against pregnancy.

V. Conclusion

For decades, thalidomide was the leper of the medical community. Ridiculed by the trade press, scorned by the majority of researchers, and feared by FDA, the drug seemed destined to live in infamy. Not until recent years was thalidomide allowed to see the light of day. Now, with FDA approval for the treatment of ENL, the irony is not lost. The question, however, remains—did FDA make the correct decision in approving thalidomide?

The costs are undoubtedly high. As was seen with the distribution of the teratogenic Accutane, some thalidomide babies will be born. Contraceptives will fail, drugs will be shared, and surprise pregnancies will occur. In Brazil, for example, affected babies continue to be born despite a nationally-run limited distribution program.[279]Are Americans prepared to watch popular press exposés on the first, second, and even third new thalidomide baby? More importantly, are they willing to pay for them? The cost of caring for disabled children and eventually disabled adults will fall not on the drug manufacturer (which is immune from liability based on the woman's informed consent) but on society.

A further cost lies in the inherent danger of an exploding off-label use system. Although approved only for ENL, physicians are permitted to conduct what are in effect their own clinical trials by prescribing the drug for different diseases. While the S.T.E.P.S.^{TM} registry will provide the name of the physician and patient,

[279]See e.g., James Cutler, Thalidomide revisited: Letter to the Editor, 343 Lancet 795-96 (1994) (revealing 46 cases of birth defects in Brazil).

it does not require a diagnosis; therefore, tracking the incidence of off-label usage would be problematic.[280] However, the therapeutic benefits of this life-saving drug far outweigh the costs associated with its use. Thalidomide has been found to be effective in treating ENL, tuberculosis, AIDS wasting and aphthous ulcers, lupus, rheumatoid arthritis, and chronic graft-versus-host-disease. The drug also shows great promise in helping in the fight against cancer, macular degeneration, TB, and Kaposi's sarcoma. In some of these diseases, thalidomide has been the only effective treatment not accompanied by horrific side effects; in others, the drug is used in combination as part of a multi-drug regiment. Ultimately, in one form or another, the drug has helped thousands of lives.

Whether it is the havoc wreaked by chemotherapy or the birth defects caused by thalidomide and Accutane, many of today's cures come with a cost. It remains the duty of the government to police the boundaries of that cost and to analyze who it is that pays. The state does have a type of moral obligation to protect, to the extent possible, the fetus. But it is important to note that in the case of thalidomide, the debate centers around a *possible* fetus, not an existing unborn child. Thalidomide can only be administered to a woman who has presented a negative pregnancy test taken within the previous twenty-four hours. Even more so than Accutane, the possibility that a thalidomide patient is pregnant when therapy begins is highly unlikely. Thus, the controversy pits the rights of a very real and ill woman against those of a hypothetical fetus.

Aside from the cost-benefit analysis, the decision to approve thalidomide was the only ethical choice. It is unfair to punish all persons by denying the general availability of a life-saving drug simply because some patients will choose not to follow the instructions. The S.T.E.P.S.^{TM} Program is designed to admit only those persons unable to become pregnant while taking thalidomide. Contraception and pregnancy testing requirements are explicitly stated and the risks to a possible fetus are conveyed to the patient

[280] The obvious way to track off-label usage would be to subtract the number of Hansen's disease patients from the number of registered thalidomide users. The difficulty lies in the fact that although there are currently an estimated 1000 Hansen's disease patients in the United States, not all leprosy patients report to the Carville center and therefore the total number at any given time is unlikely to be proven with certainty.

through discussion with the prescribing physician, written materials (including a picture-filled brochure), and even a videotape containing testimonials from thalidomide-affected members of the Thalidomide Victims Association of Canada. In the end, the patient provides what can only be called her informed consent to thalidomide treatment.

As Dr. John Fletcher argues in the context of clinical trials, it is paternalistic for the government to deny a woman the right to make her own informed choice.[281]The deference given to a woman's autonomy on other health issues should be afforded in the thalidomide context as well. For example, a woman today has control over whether she becomes and stays pregnant. American jurisprudence has protected that acknowledged privacy right for years. As Justice Blackmun so eloquently wrote in his concurring opinion to *Planned Parenthood of Southeastern Pennsylvania v. Casey*,[282] "...when the State restricts a woman's right to terminate her pregnancy, it deprives a woman of the right to make her own decision about reproduction and family planning—critical life choices that this Court has long deemed central to the right of privacy...."[283]The choice to take thalidomide implicates a woman's "decisions about reproduction and family planning"[284] and therefore should be left for her to decide.

At the end of the day, FDA is required to weigh the costs and benefits as well as the ethics involved in approving a teratogenic drug. In the case of thalidomide, FDA realized correctly that the S.T.E.P.S.™ Program represented the best means of preventing fetal exposure. Thalidomide undoubtedly will forever occupy a notorious place in history. Today, however, the drug is on the brink of a new era. As more research is conducted and novel therapeutic uses are discovered, thalidomide promises to move from a position of tragedy to one of triumph.

[281]See John C. Fletcher, Women's and Fetal Rights and Interests: Ethical Aspects, 48 Food and Drug L. J. 213, passim (1993).

[282]505 U.S. 833 (1992).

[283]Id. at 927.

[284]Id.