

## THE COST OF CLEAR SKIN: BALANCING THE SOCIAL AND SAFETY COSTS OF IPLEDGE WITH THE EFFICACY OF ACCUTANE (ISOTRETINOIN)

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The Food and Drug Administration (“FDA” “Agency”) continues to face one of the most intractable issues of its tenure: deciding whether and when efficacious treatments that may harm fetuses should be available on the market.<sup>1</sup> Currently, the Agency weighs the benefits of such medication with the risk of fetal malformation, factoring the expected reduction of risk accomplished with the utilization of risk management programs.<sup>2</sup> These risk management programs seek to decrease the occurrence of fetal exposure by facilitating the distribution of educational materials and limiting drug access among women of child-bearing age.<sup>3</sup> This is best illustrated by the current debate raging within medical circles regarding the FDA’s decision to allow Accutane and its generic equivalents<sup>4</sup> to remain on the market, while attempting the third in a series of flawed risk management programs to prevent the birth of children with disabilities due to drug exposure. As implemented, the Accutane risk management program is inadequate to accomplish its goals of eliminating fetal exposure, and represents an unacceptable incursion on women’s autonomy to decide the course of their medical care. Consequently,

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<sup>1</sup> See JEFFERY E. FETTERMAN ET AL., A FRAMEWORK FOR PHARMACEUTICAL RISK MANAGEMENT 7 (Food and Drug Law Institute 2003).

<sup>2</sup> *Id.*

<sup>3</sup> *Id.* at 7, 8.

<sup>4</sup> Throughout this Comment Accutane and its generic equivalents are collectively referred to as Accutane or isotretinoin. Since Accutane did not have generic competition until the implementation of the S.M.A.R.T. risk management program, the use of Accutane, instead of the generic name isotretinoin, after the introduction of generics is done solely to avoid confusion.

the FDA should remove Accutane and its generic equivalents from the market.

Some medications present such a serious risk to fetuses that the FDA has advised manufacturers to provide warnings accompanying the medication to ensure that pregnant women or those of child-bearing age do not take or come in contact with the drug.<sup>5</sup> Labeling warnings on products is just one mechanism advocated by the FDA to manage risk through educating patients about the drug's effect in pregnancy.<sup>6</sup> For example, Propecia, which treats hair loss in men, has such a high potential for mutative effects in fetuses that prescription bottles contain warnings alerting women who may be pregnant to avoid handling the medication if tablets are broken.<sup>7</sup>

Recently, the FDA has approved much more aggressive and formalized risk management programs like S.T.E.P.S., A System for Thalidomide Education and Prescribing Safety, to ensure the safety of pregnant women and women of child-bearing potential.<sup>8</sup> Thalido-

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<sup>5</sup> See FETTERMAN, *supra* note 1. Medications known to be teratogens and therefore contra-indicated in pregnancy include: androgens, anticonvulsants, antineoplastics, diethylstilbestol, etretinate, iodides, isotretinoin, lithium, live vaccines, methimazole, penicillamine, tetracyclines, and warfarin. JOSEPH T. DIPIRO, ET AL., PHARMACOTHERAPY 1302 (4th ed. 1999). Medications suggested to be teratogens and therefore have warnings against use in pregnancy include: angiotension converting enzyme inhibitors (ACE-I), benzodiazepines, estrogens, oral hypoglycemics, progestogens, and quinolones. The FDA has approved these medications with warnings, concerning their risk in pregnancy. *Id.*

<sup>6</sup> See FETTERMAN, *supra* note 1.

<sup>7</sup> CHARLES F. LACY, ET AL., DRUG INFORMATION HANDBOOK 481 (Lexi-Comp 2001); Merck, Propecia homepage, <http://www.propecia.com> (last visited Jan. 3, 2007). Propecia (Finasteride) is a medication useful in the treatment of male pattern baldness. *Id.*

Women who are or may potentially be pregnant must not use Propecia and should not handle crushed or broken Propecia tablets because the active ingredient may cause abnormalities of a male baby's sex organs. If a woman who is pregnant comes into contact with the active ingredient in Propecia, a doctor should be consulted. Propecia tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed.

Merck, Propecia homepage, <http://www.propecia.com> (last visited Jan. 3, 2007).

<sup>8</sup> Center for Drug Evaluation and Research, FDA Announces Approval of Drug for Hansen's Disease (Leprosy) Side Effect; Imposes Unprecedented Authority to Restrict Distribution, <http://www.fda.gov/cder/news/thalinfo/> (last visited Jan. 9, 2007).

On July 16, 1998, FDA approved the use of thalidomide for the treatment of the debilitating and disfiguring lesions associated with erythema nodosum leprosum (ENL), a complication of Hansen's Disease, commonly known as leprosy. Because of thalidomide's potential for causing birth defects, FDA invoked unprecedented regulatory authority to tightly control the marketing of thalidomide in the United States. A

midate was first marketed in Western Europe in the late 1950s for the treatment of morning sickness in pregnancy and for use as a sleeping pill.<sup>9</sup> At the time, its teratogenic effect was unknown until women exposed to the medication delivered infants with horrific birth defects, including mutation of limbs.<sup>10</sup> The FDA immediately denied approval of this drug for marketing in the United States.<sup>11</sup> In response to the appalling effects of Thalidomide, Congress enacted legislation requiring pharmaceutical manufacturers to prove the efficacy of a drug product to obtain FDA approval.<sup>12</sup>

In a remarkable turn around, in 1998 the FDA approved Thalidomide for the treatment of lesions associated with leprosy.<sup>13</sup> The FDA conditioned approval upon the manufacturer's implementation of S.T.E.P.S.,<sup>14</sup> a stringent risk management program that includes requiring female patients of reproductive age to undergo pregnancy testing and contraception counseling, the company to maintain a patient registry, and manufacturers to control distribution to authorized prescribers and pharmacies.<sup>15</sup> Thalidomide's resurgence epitomizes the challenge of balancing risks and benefits of efficacious treatments that carry significant safety risks.

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System for Thalidomide Education and Prescribing Safety (S.T.E.P.S) oversight program has been initiated that includes limiting authorized prescribers and pharmacies, extensive patient education about the risks associated with thalidomide and a 100% patient registry. This oversight program is designed to help insure a zero tolerance policy for thalidomide exposure during pregnancy.

*Id.*

<sup>9</sup> Center for Drug Evaluation and Research, Frequently Asked Questions and Answers about Thalidomide, <http://www.fda.gov/cder/news/thalinfo/> (last visited Jan. 9, 2007).

<sup>10</sup> See Janet Woodcock, FDA's Medical Review of Thalidomide Clinical Development, <http://www.fda.gov/cder/news/thalinfo/20785medr.htm> (last visited Jan. 9, 2007).

<sup>11</sup> *Id.*

<sup>12</sup> *Id.* Kefauver-Harris Drug Amendments passed to ensure that a drug was not only safe for human use but also effective in treating a proposed indication. *Id.* For the first time, drug manufacturers were required to prove to FDA the effectiveness of their products before marketing them. *Id.*

<sup>13</sup> Center for Drug Evaluation and Research, *supra* note 8.

<sup>14</sup> Letter from Murray M. Lumpkin, Deputy Center Dir., Center for Drug Evaluation and Research, to Steve Thomas, Celgene Corporation (July 16, 1998) (on file with the FDA), available at <http://www.fda.gov/cder/foi/appletter/1998/20785ltr.pdf>.

<sup>15</sup> Memorandum from Carl Kraus, Medical Officer, Division of Special Pathogen and Immunologic Drug Products, to Anne Trontell, Deputy Director, Office of Drug Safety at the Department of Health and Human Services (Jan. 29, 2004) (on file with the FDA), available at <http://www.fda.gov/ohrms/dockets/ac/04/briefing/4017B1-06b%20Overview%20STEPS%20Section%20C%20Tab%207.pdf>.

And yet, the FDA's approach only *manages* risk; it does not eliminate it. In the same year that the FDA approved S.T.E.P.S, the Agency also permitted the introduction of Accutane, a drug used to treat severe acne but shown to cause birth defects.<sup>16</sup> Six years after market introduction, Accutane's manufacturer, Hoffman-La Roche, designed the Pregnancy Prevention Program ("PPP") to prevent pregnancy exposures from Accutane in response to concerns about birth defects.<sup>17</sup> PPP required disbursement of educational materials about avoiding pregnancy while on the medication, periodic pregnancy testing, and evidence of contraceptive use or abstinence by females of child-bearing age.<sup>18</sup> The program did not yet include a mandatory patient registry or controlled distribution like S.T.E.P.S.<sup>19</sup> The inadequacy of these precautions is poignantly illustrated by events that occurred in 1999, when a twenty-five year old woman obtained a prescription for Accutane from her dermatologist for treatment of severe acne.<sup>20</sup> The patient began Accutane therapy without waiting for menstruation, as indicated in the patient literature about the program requirements for women of reproductive age.<sup>21</sup> Despite having had a negative pregnancy test before starting the medication and using two forms of contraception during sexual intercourse, the patient had a positive pregnancy test after taking the medication for one month.<sup>22</sup> Her infant was born with multiple anomalies.<sup>23</sup> After cardiac surgery and extensive medical treatment for nine weeks, the infant died.<sup>24</sup>

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<sup>16</sup> See Woodcock, *supra* note 10.

<sup>17</sup> See FDA, Background of Isotretinoin Teratogenic Risk Management Plan at 1, <http://www.fda.gov/ohrms/dockets/ac/04/briefing/4017B1-02%20AC%20Intro%20Review%20Section%20A%20Tab1.pdf> (last visited Jan. 9, 2007) [hereinafter Background of Isotretinoin]; see Eileen Enny Leach, MPH, Targeted Pregnancy Prevention Program for Women on Accutane, Presentation to the FDA (Sept. 18, 2000) available at <http://www.fda.gov/ohrms/dockets/ac/00/slides/3639s1j.ppt>.

<sup>18</sup> Leach, *supra* note 17.

<sup>19</sup> *Id.*

<sup>20</sup> See *Accutane-Exposed Pregnancies—California 1999*, 49 MORBIDITY & MORTALITY WKLY. REP. 28, 30–31 (Jan. 21, 2000) [hereinafter *Accutane-Exposed*].

<sup>21</sup> *Id.* at 29–31. Waiting until menstruation before initiating treatment is a preventative measure to confirm a woman has not conceived from the time of her pregnancy test to the first day of therapy. *Id.*

<sup>22</sup> *Id.*

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

<sup>24</sup> *Id.*

This case, which is one of many,<sup>25</sup> illustrates the grave consequences of a risk management program that fails. Failures occur most frequently because of noncompliance by the patient who neglected to read the program information and by the physician who did not counsel the patient on the program requirements.<sup>26</sup> Imposing even greater restrictions to avoid knowingly giving birth to a child with severe deformities due to drug exposure creates a proverbial Gordian knot—how does one create a program that grants access to a life-changing drug, while simultaneously regulating its use to prevent the occurrence of fetal exposure?<sup>27</sup>

This Comment analyzes the FDA's reliance on risk management programs to balance public health with patients' access to medical innovation by focusing on the most recent iteration of such programs, iPLEDGE for Accutane and its generic equivalents. Part I of this Comment provides a general review of Accutane's FDA approval history, reports of fetal harm from exposure to the drug, and past Accutane risk management programs that failed to sufficiently minimize fetal exposure. Part II is broken into two sections discussing the social and safety costs of the iPLEDGE program. The first section examines the program's implications for women of child-bearing potential. This section provides a brief history of limiting women's health care decisions based on child-bearing age and then analyzes how iPLEDGE provisions affect such women. The second section discusses the safety implications of iPLEDGE, specifically illustrating how this program will not achieve the goal set by the FDA to eliminate pregnancy exposures to Accutane. Finally, Part III concludes that iPLEDGE is inadequate for fulfilling the FDA's role in protecting public health by permitting access to unsafe medication under the guise of a counterproductive and intrusive monitoring program. Having Accutane available on the market has great social and safety costs that outweigh its effectiveness in treating severe acne. Therefore, the medication should not be available to the general public. The FDA should not allow flawed risk management systems to mask a manufacturer's inability to produce a safe product.

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<sup>25</sup> See e.g. *Accutane-Exposed*, *supra* note 20; M.A. Honein, et. al., *Continued Occurrence of Accutane-Exposed Pregnancies*, 64 *TERATOLOGY* 142, 143 (2001).

<sup>26</sup> *Accutane-Exposed*, *supra* note 20; *Continued Occurrence of Accutane-Exposed Pregnancies*, *supra* note 25, at 143.

<sup>27</sup> See Bernadine Healy, *Pledging for Accutane*, U.S. NEWS & WORLD REP., Sept. 5, 2005, at 63; Laurel N. Geraghty, *Doctors Fear Acne Drug Rules Go Too Far*, N.Y. TIMES, Jan. 12, 2006.

## I. AN OVERVIEW OF ACCUTANE'S APPROVAL HISTORY

In 1982, the FDA approved Hoffman-La Roche's ("Roche") Accutane for the treatment of severe nodular acne.<sup>28</sup> This type of acne produces cysts on the face and body from bacteria developing in increased numbers, stimulating the inflammatory process, and producing lesions with a diameter of five millimeters or greater, which can produce severe scarring.<sup>29</sup> The duration of Accutane treatment is fifteen to twenty weeks and results in partial to complete remission of cyst-forming acne.<sup>30</sup> From 1982-2000, over five million Americans took Accutane, with 19.8 million prescriptions dispensed from United States pharmacies.<sup>31</sup> Since that time, generic versions of the drug have been on the market, resulting in lower prices and greater accessibility.<sup>32</sup> While even severe acne is undeniably far from a life threatening condition, Congress heard testimony in 2002 while investigating the safety of Accutane that illustrated how life altering this treatment has been for patients.<sup>33</sup> Some patients referred to the medication as a "miracle drug."<sup>34</sup> A former Accutane patient, David Shove, recounted:

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<sup>28</sup> Center for Drug Evaluation and Research, Label and Approval History of Accutane (Isotretinoin) NDA #018662, [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label\\_ApprovalHistory#applist](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#applist) (last visited Jan. 9, 2007) (approval occurred on May 7, 1982).

<sup>29</sup> *Id.*

<sup>30</sup> *Id.*

<sup>31</sup> Diane K. Wysowski et al., *Use of Isotretinoin (Accutane) in the United States: Rapid Increase from 1992 through 2000*, 46 J. AM. ACAD. DERMATOLOGY 505, 506 (2002); Mitchell et al., *An Assessment of the Accutane Pregnancy Prevention Program*, Presentation at the FDA Dermatologic Drugs Advisory Committee Meeting (Sept. 18, 2000).

<sup>32</sup> Center for Drug Evaluation and Research, Therapeutic Equivalents of Accutane (Isotretinoin) NDA #018662, <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Generics> (last visited Jan. 9, 2007). There are currently three generic versions of Accutane, which all have the same active ingredient isotretinoin. *Id.* These generic products include: Amnesteem manufactured by Genpharm, FDA approval on Nov. 8, 2002; Claravis manufactured by Barr, FDA approval on Apr. 11, 2003; and Sotret manufactured by Ranbaxy, FDA approval on Dec. 24, 2002, Jun. 20, 2003. *Id.*

<sup>33</sup> *Issues Relating to the Safety of Accutane: Hearing Before the Subcomm. on Oversight and Investigations of the H. Comm. on Energy and Commerce*, 107th Cong. 107-143 (2002) (The investigation of Accutane by the Subcommittee was prompted after reports of birth defects, depression and suicides related the drug's use. Representative Stupak, member, House Comm. on Energy and Commerce, lost his son from suicide, possibly related to Accutane use.).

<sup>34</sup> *Id.* (statement by Dr. Diane S. Berson, Associate Director of Dermatology at Cornell University).

Accutane has been called a "miracle drug" by many patients who have suffered from the pain and embarrassment of acne. It has

I endured severe acne during my high school years. . . . I was fixated upon the idea that my classmates were consumed by my “freakish” appearance. I was embarrassed at times to be seen. I avoided all cameras . . . and image capturing experiences. I refrained from attending events during the most heinous of break-outs. I loathed the idea of presenting in front of any type of group. . . . While all these ideas may seem simple and, in the grand scheme of the universe, unimportant, I assure you to a 17-year-old growing up, one’s physical appearance is life-defining. Accutane does not grow self-confidence genes, it does not develop assertiveness cells, it simply clears one’s skin. It is through this basic task, that Accutane did, in fact, change my life.<sup>35</sup>

A. *Risk Management from Accutane Drug Approval to S.M.A.R.T. (1982-2000)*

The FDA first reviewed Accutane’s clinical data in 1981 when Roche filed a New Drug Application (NDA).<sup>36</sup> At this time, Roche submitted animal testing data to the FDA illustrating birth defects in animal offspring.<sup>37</sup> In addition, the manufacturer reported no human birth defects in clinical trials.<sup>38</sup> As a result, the manufacturer recommended that warnings be included within Accutane labeling cautioning women about this possible side effect.<sup>39</sup> However, the

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changed the lives of so many young adults who were forced to avoid interactions with their peers at the very age when association awareness peaks.

In the last 15 years I have prescribed Accutane to hundreds of patients. So many individuals are grateful that I was able to offer them medication which cleared a condition many had suffered with for years . . . .

*Id.*

<sup>35</sup> *Id.* (statement of David Shove, former Accutane patient).

<sup>36</sup> Center for Drug Evaluation and Research, *supra* note 28.

<sup>37</sup> Jill Riepenhoff & Mark D. Somerson, *Company Soft-Pedaled Accutane Tie to Birth Defects in 1982*, COLUMBUS DISPATCH, May 19, 1996, at 2D.

<sup>38</sup> *Id.*

<sup>39</sup> *Id.* Roche recommended approval of Accutane labeling with a Pregnancy category C designation. *Id.* Pregnancy category C is used “[i]f animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.” 21 C.F.R. § 201.57(c)(9)(i)(A)(3). Pregnancy category A is used “[i]f adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters) . . . .” 21 C.F.R. § 201.57(c)(9)(i)(A)(1) (2006). Pregnancy category B is used “[i]f animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women . . . .” 21 C.F.R. § 201.57(c)(9)(A)(2). Pregnancy category D is used “[i]f there is positive evidence of

manufacturer failed to inform the Agency of the precautions taken to avoid pregnancy exposure in the clinical trials.<sup>40</sup> Some clinical trials excluded women completely while others required women to be on oral contraception and undergo pregnancy testing.<sup>41</sup> One woman became pregnant but decided to have an abortion.<sup>42</sup> Unaware of these details, the FDA made no additions to the label educating women about the details of these clinical trials.<sup>43</sup> The FDA did refer the animal testing data to its Dermatologic Drugs Advisory Committee (now called the Dermatology and Ophthalmic Drugs Advisory Committee) to recommend additional pregnancy warnings.<sup>44</sup>

After reviewing the NDA and referring it to an advisory committee, the Agency approved the medication after only nine months. Due to the drug's effectiveness in the treatment of severe acne, the FDA accelerated the approval process.<sup>45</sup> Consequently, Accutane was approved in 1982.<sup>46</sup> The drug was designated a pregnancy category X medication, an FDA code indicating that the risk of the drug in pregnancy outweighs any benefit it may have.<sup>47</sup>

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human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective) . . . ." 21 C.F.R. § 201.57(c)(9)(A)(4). Finally, pregnancy category X is used "[i]f studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available) . . . ." 21 C.F.R. § 201.57(c)(9)(A)(5).

<sup>40</sup> Riepenhoff & Somerson, *supra* note 37, at 2D.

<sup>41</sup> *Id.*

<sup>42</sup> Jill Riepenhoff & Mark D. Somerson, *Patient was Urged to Get an Abortion; Researcher Feared Defects in Accutane User's Baby*, COLUMBUS DISPATCH, April 8, 1996, at 1C.

<sup>43</sup> Background of Isotretinoin, *supra* note 17, at 1.

<sup>44</sup> Dr. Colonel Evans, FDA Medical Group Leader, Speaker at the Dermatologic Drugs Advisory Committee Open Session (May 8, 1989) (transcript available at <http://www.fda.gov/ohrms/dockets/ac/accutane/29t1.pdf>).

<sup>45</sup> Penny Chorlton, *FDA Outpaced Firm on Acne Drug*, WASH. POST, Sept. 13, 1982, at 56 (Accutane had been classified by the FDA as "IA," meaning it was top priority for approval. The quick turnaround time from submission of NDA to approval surprised Roche who took an extra four months to prepare the drug for launch to the public.).

<sup>46</sup> Center for Drug Evaluation and Research, *supra* note 28 (approval occurred on May 7, 1982).

<sup>47</sup> Background of Isotretinoin, *supra* note 17, at 1; 21 C.F.R. § 201.57(c)(9)(A)(1-4).

Shortly thereafter, the company received voluntary reports of pregnancy from Accutane users and disclosed the cases to the FDA.<sup>48</sup> Consequently, the FDA advised Roche to make additions to pregnancy warnings, which included sending “Dear Doctor” letters and creating red warning stickers to be used at pharmacies to alert patients of the pregnancy risk.<sup>49</sup> Despite the effort to bolster patient warnings and make reports to doctors, the manufacturer and the FDA continued documenting instances of infants being born with Accutane embryopathy malformations.<sup>50</sup>

For example, in February of 1988, Dr. Godfrey Oakley wrote the FDA stating,

I know that because the product is effective against cystic acne that removing the drug from the market will not be popular. On the other hand, I know that 40 infants born alive after the first trimester exposure to Accutane have died as infants or children because of the developmental errors that Accutane caused. I believe if 40 teenagers or young adults with acne had died as a result of therapy caused by this drug that the drug would [be] viewed as too dangerous, even though effective, to be on the market.<sup>51</sup>

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<sup>48</sup> Memorandum from Dr. Edward Lammer, FDA Epidemic Intelligence Service (EIS) Officer, to Drs. Godfrey P. Oakley and Jose Cordero, Centers for Disease Control staff (July 29, 1983) (on file with the FDA), *available at* <http://energycommerce.house.gov/107/hearings/12112002Hearing755/2.pdf>. The memorandum entitled “The Record (Teratology File)” describes how the FDA spoke with Roche and received reports of four cases of children born with malformations from mothers who had taken Accutane in the first trimester. The record also documented that though Roche reported in November of 1982 that:

no fetal abnormalities were reported in the Accutane clinical trials, in fact there were no outcomes to evaluate. Of the 4 pregnancies occurring during the trials, 2 women elected to abort their fetuses, one child was dead at 26 weeks gestation secondary to a prolapsed cord, and one child was delivered at term and was normal. Retrospectively, it was determined that this latter mother was noncompliant and never took the drug during her pregnancy.

*Id.* This document is then followed by countless letters from doctors asking the FDA to pull the drug off the market. *Id.*

<sup>49</sup> Background of Isotretinoin, *supra* note 17, at 1. FDA “Dear Doctor” letters are letters mailed to physicians highlighting specific information a prescriber should be aware of concerning a medication. See FDA, Manual of Standard Operating Procedures and Policies, SOPP 8108, <http://www.fda.gov/cber/regsopp/8108.htm> (last visited Jan. 7, 2007). Usually specific warnings or contraindications are emphasized in these letters. *Id.*

<sup>50</sup> Center for Disease Control and Prevention (CDC), *Current Trends Birth Defects Caused by Isotretinoin—New Jersey*, 37 MORBIDITY & MORTALITY WKLY. REP. 171–72, 177 (1988) (Embryopathy includes craniofacial, cardiac, thymic, and central nervous system malformations).

<sup>51</sup> Letter from Dr. Godfrey P. Oakley, Jr., Dir. of Div. of Birth Defects & Developmental Disabilities Ctr. for Env'tl. Health and Injury Control, Ctrs. for Disease Con-

In addition, Dr. J. David Erickson wrote a letter to the FDA illustrating the concerns of the medical community and questioning the FDA's rationale in allowing Accutane to remain on the market.<sup>52</sup> In his letter he asked, "I would like to know what procedures were followed to arrive at an accounting of the benefits and risks of the use of these drugs."<sup>53</sup>

Consequently, the FDA Dermatologic Drugs Advisory Committee met on April 26, 1988 to discuss the reaction to reports of fetal exposure and abortions associated with the use of Accutane.<sup>54</sup> At this meeting, the FDA reported knowing of sixty-two birth defects attributed to Accutane and presented evidence suggesting that the drug was being used by thousands of women of child-bearing potential with less than severe acne.<sup>55</sup> As a result, the committee recommended the FDA restrict the drug's use in one or more of the following ways: dispensing only to certain physicians, placing restrictions on medication access, or requiring educational programs for physicians to dispense the drug.<sup>56</sup> Following this meeting, the FDA suggested "a number of interventions [to Roche] the purposes of which were 1) elimination of pregnancy exposure and 2) reduction of product usage to that specified in the labeling."<sup>57</sup>

After discussions with the FDA concerning the advisory committee's suggestions, Roche introduced the PPP in 1988.<sup>58</sup> This program comprised of package warning labels, an informed consent form, an informational kit for prescribers, a tracking study to assess prescribers' use of the kit, and a voluntary patient enrollment survey (the Bos-

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trol, to Dr. Gerald Faich, FDA staff (Feb. 1, 1988) (on file with the FDA), *available at* <http://energycommerce.house.gov/107/hearings/12112002Hearing755/3.pdf>.

<sup>52</sup> Letter from Dr. J. David Erickson, Chief, Birth Defects and Genetic Diseases Branch, Div. of Birth Defects & Developmental Disabilities at the Ctr. for Evtl. Health and Injury Control, Ctrs. for Disease Control, to Dr. James Bilstad, FDA Staff (Mar. 17, 1988) (on file with the FDA), *available at* <http://energycommerce.house.gov/107/hearings/12112002Hearing755/4.pdf>.

<sup>53</sup> *Id.*

<sup>54</sup> FDA, Isotretinoin (Accutane) Birth Defects Update at 1, Apr. 26, 1988, <http://www.fda.gov/bbs/topics/ANSWERS/ANS00247.html> (last visited Jan. 9, 2007).

<sup>55</sup> *Id.* at 1.

<sup>56</sup> *Id.* at 2.

<sup>57</sup> Memorandum from Dr. David J. Graham, Medical Epidemiologist, Accutane Monitoring Group, Dep't of Health and Human Services, to the Chairman of the Accutane Monitoring Group, Dep't of Health and Human Ser. at 1 (Apr. 6, 1989) (on file with the FDA), *available at* <http://energycommerce.house.gov/107/hearings/12112002Hearing755/9.pdf>.

<sup>58</sup> Leach, *supra* note 17, at 1; Background of Isotretinoin, *supra* note 17, at 1.

ton University Accutane Survey)<sup>59</sup> to assess compliance with the program.<sup>60</sup> The change in the medication's labeling required women of child-bearing potential desiring a prescription for Accutane to commit either to abstaining from sexual intercourse, or to using two methods of effective contraception simultaneously, to have a negative pregnancy test before starting Accutane, and to wait until the second or third day of their next menstrual period before beginning to take Accutane.<sup>61</sup> In addition, women were required to undergo monthly pregnancy testing and monthly contraceptive counseling while on Accutane therapy.<sup>62</sup> Doctors could only prescribe a month supply of Accutane to enforce continued evaluation and counseling of patients.<sup>63</sup>

Yet, even with this program, reports of fetal exposure to Accutane continued. In an April 1989 FDA memorandum, Dr. David Graham reported the incidence of pregnancy exposure based on reports of at least one pregnancy per 2000 women of reproductive age.<sup>64</sup> Dr. Graham also acknowledged FDA discrepancies in pregnancy exposure data—"the FDA learned only a fraction of actual first trimester pregnancy exposure events."<sup>65</sup> Furthermore, Graham observed that such underreporting is common with Accutane because "the majority of Accutane pregnancy exposures end with either spontaneous or induced abortion and physicians do not customarily report such outcomes as adverse drug reactions."<sup>66</sup> In addition, Dr. Graham articulated concern about the lack of effective, post-marketing studies by Roche to evaluate the effectiveness of the new labeling change.<sup>67</sup>

A year later, Dr. Graham reported the past two years illustrate "that intensive regulation has not, cannot and will not achieve the

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<sup>59</sup> Allen A. Mitchell et al., *A Pregnancy-Prevention Program in Women of Childbearing Age Receiving Isotretinoin*, 333 NEW ENG. J. MED. 101, 101-05 (July 1995) (summarizing the Boston University Accutane Survey also referred to as the Slone Survey).

<sup>60</sup> Leach, *supra* note 17. Accutane was packaged in blister packages of ten, twenty, and forty milligram tablets with an "avoid pregnancy logo at each pill site." *Id.* The package also included the black box warning concerning birth defects and line drawings of birth defects. *Id.*

<sup>61</sup> *Id.* This is to assure that the woman is not pregnant. *Id.*

<sup>62</sup> *Id.*

<sup>63</sup> Leach, *supra* note 17.

<sup>64</sup> Graham, *supra* note 57, at 1.

<sup>65</sup> *Id.* at 7.

<sup>66</sup> *Id.*

<sup>67</sup> *Id.* at 8.

Agency's goal of eliminating pregnancy exposure to Accutane."<sup>68</sup> He further argued that the drug should be immediately removed from the market citing that in the past year "while the Agency waited for more complete data on the effect of its interventions to accumulate, an additional 1900 pregnancy exposures occurred with 1500 abortions and 117 children with birth defects."<sup>69</sup> Despite this memorandum and pressure from other medical research groups, including the Centers for Disease Control and Prevention advocating the removal of Accutane from the market, the FDA continued discussions with Roche, keeping the drug on the market.<sup>70</sup>

Nearly ten years later, the Roche post-marketing studies were published with data on the effectiveness of the FDA interventions.<sup>71</sup> The January 2000 issue of *Morbidity and Mortality Weekly Report* conveyed details of the Boston University Accutane Survey.<sup>72</sup> The survey described 900 women who became pregnant while taking Accutane between 1989 and 1998, a rate of three pregnancies for every 1000 treatments with the drug.<sup>73</sup> In addition, the survey concluded a reduced pregnancy rate in 1998 of 2.1 pregnancies per 1000 females of child-bearing age versus in 1989 a rate of 4.0 per 1000.<sup>74</sup> Therefore, one could infer that PPP was effective in lowering pregnancy rates among women of child-bearing potential using Accutane. Difficulties with the study, however, caution against such a conclusion—the survey was voluntary and struggled to recruit females to participate—

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<sup>68</sup> Memorandum from Dr. David J. Graham, Section Chief, Epidemiology Branch of the FDA to Dir., Div. of Anti-Infective Drug Prod., Dept. of Health and Human Serv. at 1 (May 7, 1990) (on file with FDA), *available at* <http://energycommerce.house.gov/107/hearings/12112002Hearing755/12.pdf>.

<sup>69</sup> *Id.* at 2.

<sup>70</sup> *See id.*; Memorandum from Bob Nelson, Member of Accutane Monitoring Group to Jim Bilstad, FDA Staff (Feb. 19, 1991), *available at* <http://energycommerce.house.gov/107/hearings/12112002Hearing755/13.pdf> (describing continuing communications between the FDA and Roche regarding Accutane monitoring); Mark D. Somerson, *Memos Bare FDA Split Over Accutane*, COLUMBUS DISPATCH, July 14, 1996, at 7C (reporting that the FDA and Roche met twenty-three times between 1982 and 1991 to discuss Accutane).

<sup>71</sup> *Accutane-Exposed*, *supra* note 20, at 28–31 (reporting unpublished 1999 data from the Boston University Accutane Survey); Nelson, *supra* note 70, at 1–4 (reporting slow progress enrolling patients in the study probably due to it being a volunteer survey).

<sup>72</sup> *Accutane-Exposed*, *supra* note 20, at 28–31.

<sup>73</sup> *Id.*

<sup>74</sup> *Id.* (data implies that PPP was effective in lowering the rate of pregnancies).

therefore it did not provide an accurate comparison of pregnancy rates.<sup>75</sup>

During this same time, Accutane's popularity was growing exponentially, largely due to Roche's advertising as well as doctors over-prescribing the medication.<sup>76</sup> According to the Centers for Disease Control and Prevention's study ("CDC study"), the number of "Accutane prescriptions doubled from fewer than 750,000 prescriptions in 1989 to more than 1,800,000 prescriptions in 1999" with around half of the prescriptions being written for women in both years.<sup>77</sup> Furthermore, the CDC study hypothesized that as Accutane use in women of child-bearing potential increases, more Accutane-exposed pregnancies can be expected.<sup>78</sup>

Through the Accutane survey and Roche Drug Safety database, the FDA compiled a review of individual pregnancy reports to uncover reasons for Accutane-exposed pregnancies.<sup>79</sup> According to the prescriber tracking survey, ninety-seven percent of physicians used at least one component of the PPP.<sup>80</sup> However, the FDA review uncovered instances of patient confusion about timing of pregnancy tests,<sup>81</sup> patient misunderstanding of contraceptive methods, lack of monthly pregnancy testing and contraceptive counseling, and instances of patients receiving more than a month supply of medication.<sup>82</sup> An evaluation of the reports also found the following reasons why women became pregnant: unsuccessful abstinence, ineffective or inconsistent contraception use, unexpected sexual activity, and contraceptive failure.<sup>83</sup>

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<sup>75</sup> See Nelson, *supra* note 70, at 2-3. Regardless of the study's critiques, the FDA used three pregnancies per 1000 Accutane women patients as a factor in calculating success rates of risk management programs. See *Accutane-Exposed*, *supra* note 20, at 26.

<sup>76</sup> See M.A. Honein, L.J. Paulozzi & J.D. Erickson, *Continued Occurrence of Accutane-Exposed Pregnancies*, 64 *TERATOLOGY* 142, 143 (2001).

<sup>77</sup> *Id.*

<sup>78</sup> *Id.* at 145.

<sup>79</sup> See Leach, *supra* note 17.

<sup>80</sup> *Id.*

<sup>81</sup> *Id.* The timing of a pregnancy test refers to the methods used to prevent false negatives. *Id.* This also includes having a woman wait, even if her pregnancy tests are negative, until her second or third day of menses before starting Accutane. *Id.* This is another preventive measure taken to assure a woman is not pregnant. *Id.*

<sup>82</sup> Leach, *supra* note 17.

<sup>83</sup> *Id.* According to data presented which was based on the FDA reports and Roche's database, fourteen percent of women were pregnant at the time of initial visit and twelve percent did not wait until the next menses before starting treatment. *Id.* This suggests a failure in pregnancy testing. In addition, the breakdown of pregnancy occurrences during therapy is the following: Eleven percent "reported they believed they would be able to maintain abstinence", thirty-four percent "reported

Also at this time, the FDA received individual case reports highlighting PPP's ineffectiveness due to noncompliance among both patients and physicians.<sup>84</sup> One report related to inappropriate prescribing by a physician to a thirty-five-year-old woman for the prevention of oily skin before menstruation.<sup>85</sup> The physician did not counsel her about or recommend contraception.<sup>86</sup> Though she used an intrauterine device, she became pregnant after taking Accutane for three years.<sup>87</sup> Because she had taken two doses of Accutane since her last menstrual period, she terminated the pregnancy, stating, "the sole reason for the decision was the exposure."<sup>88</sup> Another case involved a fifteen-year-old girl whose physician refilled her Accutane prescription despite her having missed the required monthly pregnancy test.<sup>89</sup> Her pregnancy was confirmed at the next month's appointment.<sup>90</sup> While the patient used oral contraception previously, she was not taking any during the time of the exposed pregnancy.<sup>91</sup> The patient "elected to terminate the pregnancy, stating that Accutane exposure was a factor in her decision."<sup>92</sup>

As a result of the post-marketing studies, analysis of the data, and various discussions, the FDA Dermatologic and Ophthalmic Drugs Advisory Committee on September 18, 2000, recommended that Roche integrate an additional five components into its risk management program to further the FDA's goal in eliminating pregnancy exposures among Accutane users: adopt a heightened educational program for each patient "that includes verifiable documented written informed consent"; require "complete registration of all patients"; call for "complete registration and certification of practitioners who prescribe Accutane"; devise a comprehensive program to track fetal exposures to Accutane (and outcomes), including a formal mandatory pregnancy registry; and "link dispensing of Accutane to

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failure to use contraception on the perceived day of conception" (thirty-three percent of these patients were only using one form of contraception), and fifty-one percent "reported contraception failure" (sixty-one percent of these patients were using one form of contraception). *Id.*

<sup>84</sup> See Honein, *supra* note 76, at 146; *Accutane-Exposed*, *supra* note 20, at 29.

<sup>85</sup> Honein, *supra* note 76, at 147.

<sup>86</sup> *Id.*

<sup>87</sup> *Id.*

<sup>88</sup> *Id.*

<sup>89</sup> *Id.*

<sup>90</sup> *Id.*

<sup>91</sup> Honein, *supra* note 76, at 147.

<sup>92</sup> *Id.*

female patients [to] verification of adequate pregnancy testing.”<sup>93</sup> Concerned about infringing privacy rights and creating too cumbersome of a program,<sup>94</sup> Roche only incorporated two of these suggestions in its enhanced risk management program—S.M.A.R.T., System to Manage Accutane Related Teratogenicity.<sup>95</sup>

*B. Risk Management from S.M.A.R.T. to iPLEDGE (2001-2005)*

The FDA approved the enhanced risk management program, S.M.A.R.T., in fall 2001, and the program was put into effect by April 2002.<sup>96</sup> The FDA announced two main goals of the S.M.A.R.T. program: that no pregnant woman should begin Accutane therapy and “no pregnancies should occur while a woman is taking Accutane.”<sup>97</sup> The FDA indicated that even a single fetal exposure would be unacceptable, yet both the Agency and Roche recognized that the goal of eliminating all fetal exposure might not be possible.<sup>98</sup> The FDA did not set specific benchmarks in its approval of the program, but instead informed Roche that “[t]he adequacy of S.M.A.R.T. will be a review issue for re-evaluation on a continuing basis.”<sup>99</sup> Emphasizing that Roche did not incorporate all of the FDA advisory committee recommendations,<sup>100</sup> the Agency accepted this pregnancy prevention

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<sup>93</sup> Letter from Dr. Janet Woodcock, Dir., Ctr. for Drug Eval. and Research, to Dr. Russell Ellison, Chief Med. Officer, Vice President, Med. Affairs, Hoffman-La Roche, Inc. (Oct. 6, 2000), *available at* <http://energycommerce.house.gov/107/hearings/12112002Hearing755/24.pdf>; Background of Isotretinoin, *supra* note 17, at 1.

<sup>94</sup> Background of Isotretinoin, *supra* note 17, at 2.

<sup>95</sup> See Hoffman-La Roche, *Accutane Label Revision* at 9–10 (Oct. 30, 2001) (on file with the FDA), *available at* <http://www.fda.gov/cder/foi/label/2001/18662s44lbl.pdf>; Letter from Dr. Jonathan K. Wilkin, Dir., Div. of Dermatologic & Dental Drug Prod., Ctr. for Drug Eval. and Research (CDER) to Joanna Waugh, Group Dir., Drug Regulatory Affairs, Hoffman-La Roche, Inc. (Oct. 30, 2001) (on file with the FDA), at 2, *available at* <http://www.fda.gov/cder/foi/appletter/2001/18662s44ltr.pdf>.

<sup>96</sup> Hoffman-La Roche, *Accutane Label Revision* (Oct. 30, 2001) (on file with the FDA), *available at* <http://www.fda.gov/cder/foi/label/2001/18662s44lbl.pdf>; see Background of Isotretinoin, *supra* note 17, at 3.

<sup>97</sup> FDA Talk Paper, *FDA Announces Changes to the Risk Management Program to Prevent Birth Defects Caused by Accutane*, <http://www.fda.gov/bbs/topics/ANSWERS/2001/ANS01113.html> (last visited Jan. 9, 2007) [hereinafter *Changes to Risk Management Program*].

<sup>98</sup> Wilkin, *supra* note 95, at 2. The FDA indicated that no threshold for the number of fetal exposure (greater than zero) would be acceptable during the first year of S.M.A.R.T. *Id.*

<sup>99</sup> *Id.*

<sup>100</sup> See Background of Isotretinoin, *supra* note 17, at 2–3. The manufacturer indicated various reasons for its denial of the committee recommendations. See *id.* These included rejecting a patient registry because of patient privacy issues, disagreeing with certifying physicians since the manufacturer felt it had no authority to cer-

system contingent upon successful assessment studies, specifically mentioning achieving greater or equal to sixty percent enrollment in the volunteer patient survey of female patients and near 100% compliance with the various program provisions.<sup>101</sup>

The S.M.A.R.T program was unique in its attempt to remedy noncompliance by both physicians and patients. To address physicians' failure to obtain pregnancy testing, S.M.A.R.T. labeling of Accutane required that a woman of child-bearing potential have two negative pregnancy tests prior to starting treatment.<sup>102</sup> To ensure compliance, doctors had to place yellow self-adhesive Accutane Qualification Stickers on Accutane prescriptions before a pharmacist could legally fill them.<sup>103</sup> In order for a doctor to obtain these stickers, physicians had to read an informational booklet about S.M.A.R.T. and return a completed Letter of Understanding to Roche confirming comprehension of the program requirements and Accutane's risk in pregnancy.<sup>104</sup> This qualification sticker step required physicians to assess Accutane patients before each new and refilled prescription.<sup>105</sup>

In addition, S.M.A.R.T. required patients to sign informed consent forms containing warnings about fetal exposure to the drug.<sup>106</sup> Women of child-bearing potential had to commit to using two forms

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tify prescribers, and opposing a comprehensive program to track fetal exposures to Accutane because of privacy concerns. *See id.*

<sup>101</sup> *Id.*

<sup>102</sup> Hoffman-La Roche, *Accutane Label Revision* (Oct. 30, 2001) (on file with the FDA), available at <http://www.fda.gov/cder/foi/label/2001/18662s44lbl.pdf>.

[Female patients of childbearing potential] [m]ust have had two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Accutane prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for Accutane. The second pregnancy test (a confirmation test) should be done during the first five days of the menstrual period immediately preceding the beginning of Accutane therapy. For patients with amenorrhea, the second test should be done at least 11 days after the last act of unprotected sexual intercourse (without using 2 effective forms of contraception). Each month of therapy, the patient must have a negative result from a urine or serum pregnancy test. A pregnancy test must be repeated every month prior to the female patient receiving each prescription.

*Id.* at 2-3.

<sup>103</sup> *Id.* at 2. The doctor must indicate on the sticker the patient's gender, cut-off date for filling the prescription, and up to a thirty-day supply of the medication with no refills. If the patient was a woman, the doctor must, in addition, write the date of qualification as determined from the last pregnancy test taken. *Id.*

<sup>104</sup> *Id.*

<sup>105</sup> *Id.*

<sup>106</sup> Hoffman-La Roche, *supra* note 102, at 2.

of effective contraception<sup>107</sup> simultaneously unless they committed to “absolute abstinence.”<sup>108</sup> Under this new program, all women underwent monthly pregnancy tests while on Accutane therapy along with monthly consultation about contraception and behaviors associated with an increased risk of pregnancy.<sup>109</sup> To track the program’s effectiveness, the FDA required the manufacturer to conduct follow-up studies and to report the adequacy of the program to the Agency after the first year of implementation.<sup>110</sup>

Further complicating matters, by the time S.M.A.R.T. was put into effect in April of 2002, Roche’s patent had expired and two generic medications had entered the market.<sup>111</sup> Amnesteem manufactured by Genpharm was placed on the market on November 2002 and Sotret, manufactured by Ranbaxy, was approved in December 2002.<sup>112</sup> Similar to Accutane, these forms of isotretinoin were approved with accompanying risk management programs, all possessing the essential elements of Accutane’s S.M.A.R.T. program.<sup>113</sup> Nonetheless, the medical community’s concern with the risk of Accutane-exposed pregnancies increased as these more affordable generic versions became available. A comment in a Canadian medical journal was typical: “[t]he introduction of generic forms of isotretinoin, together with decreasing prices, will further increase the use of this drug by sexually active women.”<sup>114</sup>

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<sup>107</sup> *Id.* at 3. Effective forms of contraception include both primary and secondary forms of contraception. Primary forms include: tubal ligation, partner’s vasectomy, intra-uterine devices, birth control pills, and topical/implantable/insertable hormonal birth control products. *Id.* Secondary forms of contraception include diaphragms, latex condoms, and cervical caps; each must be used with a spermicide. *Id.*

<sup>108</sup> *Id.* “Absolute abstinence” is the wording taken directly from the package label, implying the patient will be compliant in her pledge to abstain from sexual intercourse. *See id.*

<sup>109</sup> Hoffman-La Roche, *supra* note 102.

<sup>110</sup> *Id.* at 10–12.

<sup>111</sup> Gideon Koren, Marina Avner & Neil Shear, *Generic Isotretinoin: A New Risk for Unborn Children*, 170 CAN. MED. ASS’N J. 1567, 1567–68 (2004).

<sup>112</sup> *Id.*; Center for Drug Evaluation and Research, *supra* note 32.

<sup>113</sup> Koren et. al., *supra* note 111. Celegene, the manufacturer of Thalomid, branded Thalidomide and obtained patents for the creation of S.T.E.P.S. *Id.* In order for Accutane and generic equivalents to use a similar risk management program, isotretinoin manufacturers licensed the risk management programs from Celegene. *Id.* Without getting into patent infringement details, isotretinoin companies were able to form similar programs without the risk of infringing S.T.E.P.S. *Id.* at 1568. These generic companies followed Hoffman-La Roche’s lead by adopting the essential elements of the S.M.A.R.T. system for their products. *Id.*

<sup>114</sup> *Id.*

These concerns proved valid. The FDA estimated total actual pregnancy exposures during the first year of S.M.A.R.T. at 548.<sup>115</sup> The S.M.A.R.T. post-marketing survey results reported a pregnancy rate of 3.5 out of 1000 female patients of child-bearing potential.<sup>116</sup> In sum, the S.M.A.R.T. program did not achieve its two goals. More strikingly, the pregnancy rates post-S.M.A.R.T. remained similar to the pre-S.M.A.R.T. rates.<sup>117</sup>

The House of Representatives Committee on Energy and Commerce addressed issues relating to Accutane safety on December 11, 2002, hearing testimony about the benefits of the drug in cases of severe acne along with reports regarding the drug's horrific effect in pregnancy as well as alleged links to depression and suicide.<sup>118</sup> Congressional and media attention along with case reports of S.M.A.R.T.'s ineffectiveness prompted a joint meeting on February 26 and 27, 2004, of the Dermatology and Ophthalmic Drugs and Drug Safety and Risk Management FDA Advisory Committees.<sup>119</sup> The

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<sup>115</sup> Drs. Sidney M. Wolfe & Sherri Shubin, Pub. Citizen's Res. Group, Presentation to the FDA Drug Safety and Risk Mgmt. and Dermatologic and Ophthalmic Advisory Comms. (Feb. 26, 2004), *available at* [http://www.fda.gov/ohrms/dockets/ac/04/slides/4017OPH1\\_01\\_Wolfe.ppt](http://www.fda.gov/ohrms/dockets/ac/04/slides/4017OPH1_01_Wolfe.ppt). This pregnancy exposure estimation is 4.6 times higher than the 120 pregnancies spontaneously reported to the FDA. *Id.* Numerical data used in the PowerPoint slide entitled "Estimation of Total Pregnancy Exposures During First Year S.M.A.R.T." was taken from an FDA report. *Id.*

<sup>116</sup> Allen Brinker, Cynthia Kornegay & Parivash Nourjah, *Trends in Adherence to a Revised Risk Management Program Designed to Decrease or Eliminate Isotretinoin-Exposed Pregnancies*, 141 ARCH DERMATOLOGY 563, 568 (2005). Enrollment for the S.M.A.R.T. post-marketing survey began six months after the initiation of S.M.A.R.T. *Id.*

<sup>117</sup> Background of Isotretinoin, *supra* note 17, at 4. ("Regarding fetal exposures, although elimination of all exposures is the goal of the risk management program, it was understood that achievement of this might not be possible. Hence no threshold for the number of fetal exposures (greater than zero) that would be 'acceptable' during the first year of S.M.A.R.T. implementation was prespecified.")

<sup>118</sup> See *Issues Related to the Safety of Accutane*, *supra* note 33. Representative Bart Stupak of Michigan's First Congressional District and member of the House Committee of Energy and Commerce lost his son to suicide in May of 2000. His son was taking Accutane. The FDA, in February of 1998, stated in a memorandum the adverse events that had been reported from the use of Accutane. The memorandum showed that there were thirty-one cases of suicide, suicide attempt or suicide ideation that were associated with the use of Accutane. Of that number, twelve were suicides, nine of them male, two female, and one unknown, and the median age was seventeen. The average onset of the suicidal event was eighty-eight days after the patient had started on the prescribed use of Accutane. As the FDA memorandum stated: "[f]or the majority, there was no antecedent history of depression, and the patients were not noted or known to be depressed at the time period prior to their suicide." *Id.*

<sup>119</sup> Letter from Dr. Jonca Bull, Dir., Office of Drug Eval. of CDER & Dr. Anne Trontell, Deputy Dir., Office of Drug Safety of CDER, to Dermatology and Ophthalmic Drugs and Drug Safety and Risk Mgmt. Advisory Comm. members and guests

committees looked at prescription compliance and patient surveys, concluding that isotretinoin-exposed pregnancies continue to occur even after the implementation of S.M.A.R.T.<sup>120</sup> While data from Roche showed better percentages in its patients and physicians' compliance, pregnancies continued to occur at an alarmingly high rate.<sup>121</sup> With an observed pregnancy rate of 3.5 to 1000, it appeared that S.M.A.R.T.'s results were similar to those reported before the program was put into place.<sup>122</sup> One presenter summarized her view:

The S.M.A.R.T. program is clearly a failure. . . . It is time to end the more than twenty years of voluntary restrictions that have failed to reduce its prescribing for more than twenty times as many women as would be using the drug if it were limited to the approved indications.<sup>123</sup>

After reviewing the data, the advisory committees recommended strengthening the risk management program to include mandatory registration of all prescription recipients and to make a negative pregnancy test a condition to prescription dispensing for female patients who can become pregnant.<sup>124</sup> Heeding the committees' recommendation, Roche and generic companies created the iPLEDGE program.<sup>125</sup> The FDA approved the program on August 15, 2005.<sup>126</sup>

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(Feb. 2, 2004) (on file with FDA), *available at* <http://www.fda.gov/ohrms/dockets/ac/04/briefing/4017B100%20Bull%20Trontell%20cover%20letter%20.pdf>.

<sup>120</sup> FDA, Dermatology and Ophthalmic Drugs and Drug Safety and Risk Mgmt. Advisory Comm. (Feb. 26 2004), *available at* <http://www.fda.gov/oc/advisory/acalendar/2004/cder12535dd02262704.html>.

<sup>121</sup> Results from Accutane Survey—Abstracted from Roche Quarterly Report Submission (Jun. 30, 2002), *available at* <http://energycommerce.house.gov/107/hearings/12112002Hearing755/52.pdf>. The compliance data illustrates: signed consent form ninety-five percent (compared to eighty-nine percent pre-S.M.A.R.T.), postponed Accutane until results of pregnancy test known eighty-nine percent (compared to seventy-eight percent pre-S.M.A.R.T.), postponed Accutane until next menstrual period fifty-one percent (compared to forty-six percent pre-S.M.A.R.T.), and pregnancy test taken prior to starting Accutane ninety-two percent (compared to eight-four percent pre-S.M.A.R.T.). *Id.*

<sup>122</sup> Dr. Allen Brinker, Isotretinoin Pregnancy Prevention Program Evaluation, Presentation to FDA (Feb. 26, 2004) (on file with FDA), *available at* [http://www.fda.gov/ohrms/dockets/ac/04/slides/4017S1\\_07\\_Brinker.ppt](http://www.fda.gov/ohrms/dockets/ac/04/slides/4017S1_07_Brinker.ppt).

<sup>123</sup> See Wolfe & Shubin, *supra* note 115.

<sup>124</sup> FDA, Dermatology and Ophthalmic Drugs and Drug Safety and Risk Mgmt. Advisory Comm. (Feb. 27 2004) (on file with FDA), *available at* <http://www.fda.gov/ohrms/dockets/ac/04/transcripts/4017T2.htm>.

<sup>125</sup> The companies filed a supplemental new drug application (SNDA) under 21 CFR § 314.520, with restrictions to assure safe use. This regulation acknowledges that while Accutane is safe and effective for some patients it imposes a risk to others. It also enables drug companies to keep their products on the market by restricting distribution of the drug to a patient population that will benefit from the drug's therapeutic effectiveness while diminishing the occurrence of the drug's side effect.

iPLEDGE, the third-generation of an Accutane risk management program, tracks the distribution of Accutane by requiring that only wholesalers registered with iPLEDGE can obtain isotretinoin from the manufacturers and only registered pharmacies can receive medication from these registered wholesalers.<sup>127</sup> In addition, only doctors registered with the program can prescribe the medication.<sup>128</sup> For prescribers to register in the program, the doctor must agree to be responsible for pregnancy counseling of female patients of child-bearing potential, as detailed in the guide for practitioners.<sup>129</sup> Prescribers also must obtain and enter patient information into the iPLEDGE system (via the internet or phone) before writing a prescription.<sup>130</sup> For women of child-bearing potential, the doctor must record monthly pregnancy test results, confirm that the patient received monthly counseling, and enter the patient's two chosen forms of contraception each month into the iPLEDGE database.<sup>131</sup>

Female patients of reproductive age must also register with the iPLEDGE program and access the system monthly to answer questions about the program requirements and to input their two chosen forms of birth control.<sup>132</sup> These women also must sign a specific informed consent about birth defects before starting isotretinoin therapy.<sup>133</sup> This form is in addition to the general informed consent form that all isotretinoin patients must sign.<sup>134</sup> The informed consent pertaining to birth defects is comprised of thirteen affirmative state-

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21 C.F.R. § 314.520 (2000); Letter from Dr. Florence Houn, Dir., Office of Drug Eval. III of CDER, to Ellen Carey, Senior Program Manager of Hoffman-La Roche (Aug. 12, 2005) (on file with FDA), *available at* <http://www.fda.gov/cder/foi/appletter/2005/018662s056ltr.pdf>.

<sup>126</sup> Letter from Dr. Florence Houn, *supra* note 125.

<sup>127</sup> Center for Drug Evaluation and Research, Label of Accutane (Isotretinoin) NDA #018662 at 19, 23, <http://www.fda.gov/cder/foi/label/2005/018662s056lbl.pdf> (last visited Jan. 9, 2007). The iPLEDGE program is detailed in the label of Accutane as well as the generic equivalents. iPLEDGE program website, <https://www.ipledgeprogram.com/> (last visited November 16, 2006). iPLEDGE is the risk management program for all isotretinoin products and therefore the iPLEDGE database is operated by a collaboration of these manufacturers. *Id.*

<sup>128</sup> Center for Drug Evaluation and Research, *supra* note 127, at 20–22.

<sup>129</sup> *Id.*

<sup>130</sup> *Id.*

<sup>131</sup> *Id.* The two forms of contraception mentioned include the choice of abstinence. *Id.*

<sup>132</sup> *Id.* at 23.

<sup>133</sup> Center for Drug Evaluation and Research, *supra* note 127, at 23.

<sup>134</sup> *Id.* at 23, 36–39. There are twelve questions in the general informed consent where a patient must acknowledge the drug's side effects. The questions mainly pertain to reporting and identifying symptoms of depression while on the medication, and reading and understanding the patient educational material. *Id.* at 36–39.

ments, next to which the patient must initial her name.<sup>135</sup> Examples of these statements are:

3. I understand that I *must* avoid sexual intercourse completely, or I *must* use 2 separate, effective forms of birth control (contraception) at the same time.

...

11. I must stop taking isotretinoin right away and *call my doctor if* I get pregnant, miss my expected menstrual period, stop using birth control, or have sexual intercourse without using my 2 birth control methods at any time.

12. . . . *If I become pregnant, I agree to be contacted by the iPLEDGE program and be asked questions about my pregnancy. I also understand that if I become pregnant, information about my pregnancy, my health, and my baby's health may be given to the maker of isotretinoin and government health regulatory authorities.* . . .<sup>136</sup>

If such a patient is under eighteen, in addition to her signature, her parent or guardian and doctor must sign the form.<sup>137</sup>

## II. THE SOCIAL AND SAFETY COSTS OF IPLEDGE

iPLEDGE permits access to medication causing severe fetal deformities<sup>138</sup> under the guise of a protective program but is in fact a counterproductive, inefficient, and intrusive monitoring system. Inexplicably, the FDA has continued to allow a medication to remain on the market with repeatedly inadequate risk management programs that fail to ameliorate the immense safety and social costs caused by Accutane.<sup>139</sup> The FDA continues to treat the risk management of Accutane like other drugs with similar risk management programs. However, such an approach is inadequate because the patient population being treated with Accutane is much broader than other medications with similar risk management programs.<sup>140</sup>

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<sup>135</sup> *Id.*

<sup>136</sup> *Id.* at 37–38 (emphasis added).

<sup>137</sup> *Id.* at 36.

<sup>138</sup> Center for Drug Evaluation and Research, *supra* note 127, at 24.

<sup>139</sup> See Background of Isotretinoin, *supra* note 17, at 1; Brinker, *supra* note 122.

<sup>140</sup> See *infra* section II.B. The FDA has approved risk management programs for other medications with the potential to cause birth defects. Thalomid is FDA approved for the treatment of severe erythema nodosum leprosum, which is a form of leprosy occurring in immunocompromised patients. Celegene, Thalomid, [http://www.thalomid.com/steps\\_program.aspx](http://www.thalomid.com/steps_program.aspx) (last visited Jan. 9, 2007). Since Thalomid has a history of horrific side effects in fetuses, the drug is managed by S.T.E.P.S. *Id.* While S.T.E.P.S. requires pregnancy testing and use of oral contraception, it does not have detailed informed consents and follow-up procedures like iPLEDGE. *Id.* Another medication with a risk management program is Tracleer, FDA approved for the treatment of pulmonary arterial hypertension. Tracleer,

The FDA articulates an unwillingness to accept a greater than zero tolerance for pregnancy rates occurring with Accutane use, yet allows the drug's existence on the market after continuously receiving reports of pregnancies under previous risk management programs.<sup>141</sup> iPLEDGE will not eliminate fetal exposures to Accutane and it does not achieve the FDA's desired balance between protecting future life and keeping an effective medication on the market.<sup>142</sup> In fact, this program implements draconian measures aimed at preventing pregnancy but creates even more problems that should be unacceptable to the FDA. The social implications of the iPLEDGE provisions on women of child-bearing potential will be explored first. Thereafter, a discussion of the safety costs associated with Accutane available on the market will be analyzed.

A. *The Social Cost of Impeding a Woman's Autonomy in Medical Treatment Decisions*

Accutane's availability through iPLEDGE promotes viewing women solely on their status as child bearers. iPLEDGE limits women's autonomy and defeats the purpose of having the medication on the market, to make available effective treatment to patients.<sup>143</sup> iPLEDGE improperly regulates a woman's choice to bear children and take the risk of having children with birth defects.<sup>144</sup> History illustrates how profound a step backward iPLEDGE takes public policy and how high a social cost it generates.

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[http://www.tracleer.com/default.asp?page=OnTrac\\_WhatsTracleer](http://www.tracleer.com/default.asp?page=OnTrac_WhatsTracleer) (last visited Jan. 9, 2007). Tracleer has a high potential for birth defects and is managed through a closed distribution system called the Tracleer Access Program (T.A.P.). Tracleer, [http://www.tracleer.com/default.asp?page=HCP\\_Prescribe](http://www.tracleer.com/default.asp?page=HCP_Prescribe) (last visited Jan. 9, 2007). T.A.P. regulates patients' access to the medication by centralizing the drug distribution to only four specialty pharmacies after a physician approves of its use in a patient. Patient Enrollment—T.A.P., <http://www.tracleer.com/dot/TAP%20Patient%20Enrollment%20Form.dot> (last visited Jan. 9, 2007).

<sup>141</sup> See Changes to Risk Management Program, *supra* note 97.

<sup>142</sup> Riepenhoff & Somerson, *supra* note 37. Due to noncompliance issues, loopholes in the iPLEDGE program and illegal use of the medication, sexually active women could use isotretinoin and become pregnant. Past risk management programs have failed. See Wilkin, *supra* note 95. iPLEDGE mandates will decrease instances of abuse but will not eliminate them. Perfection is impossible. *Id.*; See Center for Drug Evaluation and Research, *supra* note 127.

<sup>143</sup> See Center for Drug Evaluation and Research, *supra* note 127; Geraghty, *supra* note 27.

<sup>144</sup> See *Int'l Union v. Johnson Controls, Inc.*, 499 U.S. 187, 211 (1991).

i. The History of Limiting a Woman's Autonomy Based on Her Childbearing Potential

A woman's autonomy is often compromised because of her potential for pregnancy. Individual autonomy is valued as a fundamental right derived from the Constitution and generally supersedes state actions restricting such personalized freedom.<sup>145</sup> However, there are instances when even this well-protected and valued fundamental right of autonomy is sometimes limited.<sup>146</sup> The government's interest in women of child-bearing age is to protect the potential for future life.<sup>147</sup> While this interest becomes heightened when a woman is pregnant and a fetus is viable, the interest is ambiguous when a woman's rights are being limited solely based on her status as a woman of reproductive age.<sup>148</sup> Without delving into a discussion of the various contexts where a maternal-fetal conflict<sup>149</sup> arises, the following discussion will briefly highlight the treatment of women based on childbearing potential throughout history.

Historically, courts would allow limiting women from employment opportunities based on being weak and fragile, existing only to serve a domestic role and bear children.<sup>150</sup> Lawyers and lawmakers exploited perceived differences between the genders like intelligence, behavior, physical appearance, social construct, hormonal makeup, and psychological characteristics as support for treating women differently.<sup>151</sup> Ultimately, the differential treatment of women stemmed from their potential to bear children.<sup>152</sup>

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<sup>145</sup> See generally CYNTHIA DANIELS, *AT WOMEN'S EXPENSE: STATE POWER AND THE POLITICS OF FETAL RIGHTS* 24 (Harvard Univ. Press 1993).

<sup>146</sup> *Id.* at 15–35.

<sup>147</sup> *Id.*

<sup>148</sup> *Id.*

<sup>149</sup> See generally Daniels, *supra* note 145, at 24. This term refers to the relationship between a mother and fetus. *Id.* The federal government and various state governments have addressed situations where fetal rights outweigh a woman's choice. *Id.* In the context of forced medical intervention, criminal prosecution, and even abortions, there are instances where the government will interfere with the choices of a mother to protect the fetus. *Id.* Since this discussion of the social cost of iPLEDGE concerns women not yet pregnant, a discussion of the maternal-fetal context would be too broad. *Id.*

<sup>150</sup> See Julianna S. Gonen, *Removing Informed Consent from HIV Testing of Pregnant Women: A Return to the Maternal-Fetal Conflict*, 2 *GEO. J. GENDER & L.* 765, 775–76 (2001).

<sup>151</sup> *Id.* at 775–77.

<sup>152</sup> *Id.*

*Bradwell v. Illinois*<sup>153</sup> illustrates a vivid portrayal of women treated as potential child bearers. In *Bradwell*, the Supreme Court of the United States held that the right to practice law was not a privilege or immunity protected by the Fourteenth Amendment and denied a woman from obtaining a license to practice law.<sup>154</sup> Justice Bradley in his concurrence wrote, “The paramount destiny and mission of women are to fulfill the noble and benign offices of wife and mother. This is the law of the Creator. And the rules of civil society must be adapted to the general constitution of things, and cannot be based on exceptional cases.”<sup>155</sup> Thirty-five years later, a similar portrayal of women appeared in the Supreme Court case *Muller v. Oregon*.<sup>156</sup> This case denied establishing a maximum-hour law for male bakers since it interfered with the freedom to contract yet upheld such a law for women due to the government’s public interest in preserving the health of women.<sup>157</sup> The Court further stated that even when a woman is not pregnant it is imperative to safeguard her health “as healthy mothers are essential to vigorous offspring, the physical well-being of woman becomes an object of public interest and care in order to preserve the strength and vigor of the race.”<sup>158</sup>

Title VII of the Civil Rights Act of 1964 changed the analysis of the above cases, prohibiting employment discrimination on the basis of race, color, religion, sex, and national origin.<sup>159</sup> Soon afterwards, the Pregnancy Discrimination Act in 1978 was passed, extending the Title VII definition of “sex” to encompass pregnancy and related medical conditions.<sup>160</sup> However, another debate began over “fetal protection policies” instituted by employers.<sup>161</sup> These policies banned women of child-bearing potential from working with toxic substances that could affect or harm a developing fetus.<sup>162</sup>

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<sup>153</sup> 83 U.S. (16 Wall.) 130 (1873), *abrogated by* Planned Parenthood v. Casey, 505 U.S. 833, 896 (1992).

<sup>154</sup> *Id.* at 138–39.

<sup>155</sup> *Id.* at 141–42 (1873) (Bradley, J., concurring).

<sup>156</sup> *Muller v. Oregon*, 208 U.S. 412 (1908).

<sup>157</sup> *Id.* at 420–22.

<sup>158</sup> *Id.* at 421.

<sup>159</sup> 42 U.S.C. § 2000 (2000).

<sup>160</sup> *Id.* at § 2000e.

<sup>161</sup> See REGINA H. KENEN, REPRODUCTIVE HAZARDS IN THE WORKPLACE: MENDING JOBS, MANAGING PREGNANCIES 16 (Harrison Park Press 1993); SALLY J. KENNEY, FOR WHOSE PROTECTION? REPRODUCTIVE HAZARDS AND EXCLUSIONARY POLICIES IN THE UNITED STATES AND BRITAIN 12 (University of Michigan Press 1992).

<sup>162</sup> See KENEN, *supra* note 161, at 16; KENNEY, *supra* note 161, at 12.

In *International Union v. Johnson Controls, Inc.*<sup>163</sup> the Supreme Court held that sex-specific fetal-protection policies are forbidden under Title VII of the Civil Rights Act.<sup>164</sup> The case examined a battery manufacturing company's policy of excluding women of reproductive age from jobs where lead exposure was possible.<sup>165</sup> Though this case was determined in the context of employment-based discrimination, Justice Blackmun described the danger in treating all women of reproductive age as pregnant.<sup>166</sup> In addition, he mentioned that fetal safety was best left to the mother.<sup>167</sup> Addressing the disparity in treatment between women of reproductive age and other employees of the battery company, Judge Blackmun explained that the law does not accept such discrimination under Title VII.<sup>168</sup> The majority concluded by maintaining that "[i]t is no more appropriate for the courts than it is for individual employers to decide whether a woman's reproductive role is more important to herself and her family than her economic role. Congress left this choice to the woman as hers to make."<sup>169</sup>

Despite *Johnson Controls*, companies continued instituting fetal-protective policies.<sup>170</sup> While some companies felt tort liability outweighed anti-discrimination suits by keeping fetal-protective policies in place, other companies refused to acknowledge the hazards to reproduction and evaluated situations on an individualized basis.<sup>171</sup> Even still, a few companies altered their policies to facially comply with Title VII.<sup>172</sup> For example, the company Exide established a policy that required all women employees to attend a training session about lead exposure, which consisted of watching a video advocating that women should avoid jobs where exposure to lead was a possibility.<sup>173</sup> The video also explained the adverse effects of lead exposure

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<sup>163</sup> 499 U.S. 187 (1991).

<sup>164</sup> 42 U.S.C. § 2000 (2000).

<sup>165</sup> *Int'l Union v. Johnson Controls, Inc.*, 499 U.S. 187, 190 (1991).

<sup>166</sup> *Id.* at 198.

<sup>167</sup> *Id.* at 206.

<sup>168</sup> *Id.* at 210.

<sup>169</sup> *Id.* at 211.

<sup>170</sup> See Elaine Draper, *Reproductive Hazards and Fetal Exclusion Policies after Johnson Controls*, 12 STAN. L. POL'Y REV. 117, 119 (2001); Nicole G. Hoeksma, *Regulating Risk: Reproductive Toxins in the Workplace in Post-Johnson Controls Era*, 14 S. CAL. REV. L. & WOMEN'S STUD. 289, 289 (2005).

<sup>171</sup> Draper, *supra* note 170, at 121.

<sup>172</sup> *Id.*

<sup>173</sup> Suzanne U. Samuels, *The Lasting Legacy of International Union, U.A.W. v. Johnson Controls: Equal Employment and Workplace Health and Safety Five Years Later*, 12 WIS. WOMEN'S L.J. 1, 8-9 (1997).

on reproduction.<sup>174</sup> Men working at the company were never made aware of these adverse affects.<sup>175</sup>

Pharmaceutical research is another area in which women of child-bearing potential were excluded and their health disadvantaged because of their gender.<sup>176</sup> For years the FDA excluded women from clinical trials in order to protect reproductive capabilities.<sup>177</sup> This attitude of “protectionism” stemmed from a desire to avoid prior research abuse in what is frequently referred to as a “vulnerable” population.<sup>178</sup> However in 1993, President Clinton signed the National Institutes of Health Revitalization Act requiring the inclusion of women in clinical trials to ensure comprehensive analysis in research.<sup>179</sup> Consequently, the FDA policies were updated to encourage the inclusion of women participants, including those of reproductive age, in research studies.<sup>180</sup> While the Agency has not mandated that drug companies include women of child-bearing potential, the FDA has acknowledged the benefit of studying medication effects on consenting women.<sup>181</sup>

While the employment and research contexts differ from the treatment context, the issues presented in *Johnson Controls* and in the FDA’s past research policies parallel issues that arise when a woman of reproductive age is subjected to the mandates of iPLEDGE.<sup>182</sup> iPLEDGE treats women of child-bearing potential differently than other patient populations.<sup>183</sup> The program treats all women as pregnant regardless of their choice to bear children.<sup>184</sup> Instead of allowing a woman to make her own choices about contraception and the risk of pregnancy, the government and manufacturer dictate what a

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<sup>174</sup> *Id.*

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

<sup>176</sup> See FDA, FDA Scholarship in Women’s Health Program, <http://www.fda.gov/cber/clinical/femclin.htm> (last visited Jan. 9, 2007) [hereinafter FDA Scholarship]; FDA, Executive Summary—Gender Studies in Product Development, <http://www.fda.gov/womens/gender/Exec4.htm> (last visited Jan. 9, 2007) [hereinafter Executive Summary].

<sup>177</sup> See FDA Scholarship, *supra* note 176; Executive Summary, *supra* note 176.

<sup>178</sup> See FDA Scholarship, *supra* note 176; Executive Summary, *supra* note 176.

<sup>179</sup> See U.S. Department of Health and Human Services, National Institutes of Health, Revitalization Act of 1993, 42 U.S.C. § 289a-2 (2000).

<sup>180</sup> See FDA Scholarship, *supra* note 176; Executive Summary, *supra* note 176.

<sup>181</sup> See FDA Scholarship, *supra* note 176; Executive Summary, *supra* note 176. In addition, studies do not separate differential side effects on men and women, so women still are not receiving the full benefit of pharmaceutical research.

<sup>182</sup> See Draper, *supra* note 170, at 120.

<sup>183</sup> See Center for Drug Evaluation and Research, *supra* note 127.

<sup>184</sup> *Id.*

woman must do and use the iPLEDGE database to monitor compliance before allowing access to the medication.<sup>185</sup> While trying to attain a zero pregnancy exposure rate to the drug, the FDA creates a restrictive program for women that may, as a result, encourage non-compliance and increase the risk of Accutane-exposed pregnancies.<sup>186</sup>

ii. The Effect of iPLEDGE on Women of Reproductive Age

The iPLEDGE program creates several obstacles for women of reproductive age before gaining access to the medication.<sup>187</sup> While the program's goal, to reduce the risk of fetal anomalies, is laudable,<sup>188</sup> its methodology is flawed—the decisions of whether to become pregnant, how to prevent pregnancy and what risks are reasonable during pregnancy are the woman's and hers alone.<sup>189</sup> The FDA and drug manufacturers have an obligation to provide women with sufficient information to make educated decisions, but not to make the decisions for them.<sup>190</sup> iPLEDGE's imposition of restrictions on reproduction is overly inclusive in that it interferes with women's autonomy based on their *potential* to become pregnant and their *presumed* sexual activity.<sup>191</sup> The consequences of so circumscribing women's behavior and choices in their medical treatment create more harm for fertile women than if the drug was simply unavailable. Treating women as pregnant or sexually active, when they are not, and making healthcare decisions on their behalf is a backwards and unacceptable step in public policy.

iPLEDGE's impingements on a woman's freedom are both numerous and onerous. A woman of reproductive age must comply with several provisions in order to obtain a month's supply of Accutane.<sup>192</sup> At her first doctor visit, she is counseled about the birth defects that could occur if she becomes pregnant, receives a pregnancy test, is informed about registering for iPLEDGE through the electronic database, and undergoes consultation on contraception.<sup>193</sup> Regardless of her marital status, sexual orientation, personal view on

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

<sup>186</sup> *Id.* See *supra* section I.B.

<sup>187</sup> See Center for Drug Evaluation and Research, *supra* note 127.

<sup>188</sup> FDA Talk Paper, *supra* note 97.

<sup>189</sup> See DANIELS, *supra* note 145; *Int'l Union v. Johnson Controls, Inc.*, 499 U.S. 187, 210 (1991).

<sup>190</sup> See 21 C.F.R. §§ 201.56-.57 (2005).

<sup>191</sup> See Center for Drug Evaluation and Research, *supra* note 127.

<sup>192</sup> *Id.* at 23, 36–39.

<sup>193</sup> *Id.* at 21–23, 25–26, 36–39.

sex outside of marriage or intention to have children, she receives information and is counseled about contraception.<sup>194</sup>

The potential Accutane patient must then read the consent forms, which require her to initial after statements dictating what she must do when engaging in sexual activity and when faced with a pregnancy.<sup>195</sup> One statement requires her to tell the doctor at any instance she breaks her commitment of abstinence or fails to use two forms of contraception during sexual activity.<sup>196</sup>

Afterward, the woman must return to her doctor for another visit to take a second pregnancy test, confirm her initiation of treatment and receive an Accutane prescription that is voidable if not filled within seven days.<sup>197</sup> Before filling the medication, the patient must input her two forms of contraception or commitment to abstinence into the iPLEDGE database and answer questions related to the program.<sup>198</sup> This database can be accessed online or via telephone, and a woman is expected to answer and input personal information into an automated system, with no personal contact with a healthcare professional.<sup>199</sup> Only after inputting this information within the database is her prescription activated.<sup>200</sup> She must then repeat this process for refills.<sup>201</sup>

These time-consuming and private steps disregard patient-specific issues related to women of child-bearing age.<sup>202</sup> Such steps deter women of reproductive age who genuinely could benefit from taking the medication from obtaining it.<sup>203</sup> Below are examples of how this program unfairly treats women as “pregnant,” disregarding

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<sup>194</sup> *Id.*

<sup>195</sup> *Id.* at 21–23, 36–39.

<sup>196</sup> *Id.* at 38–39.

<sup>197</sup> See Center for Drug Evaluation and Research, *supra* note 127, at 21, 38.

<sup>198</sup> *Id.* at 23, 39. No information is available on how detailed these questions will be or whether some questions might offend women who have pledged to abstain from sexual intercourse or minors. See *id.*; iPLEDGE program website, *supra* note 127.

<sup>199</sup> See *id.* at 23, 46; iPLEDGE Program Frequently Asked Questions, <http://www.fda.gov/cder/drug/infopage/accutane/FAQ200610.pdf> (last visited Jan. 9, 2007) at 2–3.

<sup>200</sup> See Center for Drug Evaluation and Research, *supra* note 127, at 23, 46; iPLEDGE Program Frequently Asked Questions, *supra* note 199, at 2–3.

<sup>201</sup> Center for Drug Evaluation and Research, *supra* note 127, at 23, 38–39. Normal duration of treatment is fifteen to twenty weeks, so refills are needed. In order to obtain a refill prescription, a woman has to repeat all the program steps except signing the informed consent forms completed during her initial consultation. *Id.* at 15.

<sup>202</sup> See *supra* notes 193–202.

<sup>203</sup> *Id.*

their choices about reproduction and sexual activity in order to eradicate the possibility of pregnancy exposure to Accutane. Consequently, the premise of the program's existence, to keep an effective acne treatment on the market, is expunged when patients who could benefit from its use do not have access to it. As a result, noncompliance becomes an easy alternative for these women to gain access, increasing the possibility of Accutane-exposed pregnancies.<sup>204</sup>

### 1. A Woman Who Pledges Abstinence

A vivid example of iPLEDGE disregarding female autonomy in health decisions related to reproduction and sex is the case of a woman or young teen who pledges abstinence by religious conviction or lifestyle choice. Through iPLEDGE, she is still required to be counseled on contraception at the initial visit and monthly thereafter.<sup>205</sup> She must also undergo initial and monthly pregnancy testing.<sup>206</sup> In addition, she is required to answer questions about the program monthly that may relate to sexual activity.<sup>207</sup> This government mandated program forces a woman to hear instruction about activities and preventative measures that may contradict her faith or personal preference.

For example, the compelled use of two forms of contraception violates the religious beliefs of Catholics who adhere to church teachings that they may only use natural family planning.<sup>208</sup> Therefore, the program is an impediment for accessing isotretinoin. While a patient unable to adhere to the conditions can always choose other acne treatments for nodular acne, isotretinoin is the most effective medication on the market.<sup>209</sup> A woman who commits to abstinence is deterred from treatment by the program's rigid and possibly offensive provisions.<sup>210</sup> To subject such a woman to these mandates is bad public policy because the program precludes her from exercising her choice to become pregnant and employs contraceptive approaches

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<sup>204</sup> See *supra* section I.B.

<sup>205</sup> Center for Drug Evaluation and Research, *supra* note 127, at 21.

<sup>206</sup> *Id.*

<sup>207</sup> *Id.*

<sup>208</sup> 10 NEW CATH. ENCYCLOPEDIA 176–79 (Thomas Gale ed., Catholic University 2003). According to the labeling, natural family planning is not considered one of the options for contraception. Center for Drug Evaluation and Research, *supra* note 127, at 21–22, 37.

<sup>209</sup> See Chorlton, *supra* note 45; Center for Drug Evaluation and Research, *supra* note 28 (approval occurred on May 7, 1982, which was a fast tracked approval due to the drug's clinical effectiveness).

<sup>210</sup> See *supra* notes 193–202.

that offend her religious beliefs.<sup>211</sup> This program requires a woman who pledges abstinence to undergo additional pregnancy testing, doctor visits, and potentially offensive educational sessions.<sup>212</sup>

## 2. A Sexually Active Woman

Another implication of iPLEDGE is the effect it has on sexually active women, treating them as potentially pregnant. A woman who engages in sexual intercourse should not be compelled to forego health decisions regarding sex and reproduction as a condition of having access to medical care. To obtain Accutane, a woman engaged in sexual activity must use two forms of contraception.<sup>213</sup> This limits the woman's choices regarding her own health. For example, if a woman does not agree with or has difficulty with taking hormonal contraception, she may be prevented from access to Accutane.<sup>214</sup>

If a woman elects to take Accutane, which requires her to consent to iPLEDGE provisions, but then chooses for whatever reason not to comply with the contraception requirements, or has a contraceptive failure and becomes pregnant, she must include the iPLEDGE program in discussions regarding her personal choices.<sup>215</sup> By the program's involvement in tracking the pregnancy<sup>216</sup> and providing educational services, a woman's decision about reproduction may be influenced by a governmentally approved program. Usually the woman and her doctor discuss this decision. The fear of involving an unwanted but interested third party creates the potential for abuse in affecting a person's choice. A possible concern here could be an opportunity for the program or the FDA to advocate for abortions, thereby reducing the number of birth defects and pregnancy exposures to Accutane and keeping the drug on the market. While only a possibility, the involvement of individuals other than those whom the woman chooses raises concerns about the type of information provided to, and influences imposed upon, the patient.

## 3. A Female Minor of Child-bearing Age

Similarly, a female minor of reproductive age may be discouraged from obtaining treatment due to implications regarding parental consent. A female patient of child-bearing age, but under the age

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<sup>211</sup> See *Int'l Union v. Johnson Controls, Inc.*, 499 U.S. 187, 200 (1991).

<sup>212</sup> See Center for Drug Evaluation and Research, *supra* note 127, at 21–22, 37, 39.

<sup>213</sup> *Id.*

<sup>214</sup> *Id.*

<sup>215</sup> *Id.* at 39.

<sup>216</sup> *Id.*

of eighteen, must have her guardian or parent and doctor sign the iPLEDGE informed consent forms before initializing acne treatment.<sup>217</sup> This requires a minor not only to discuss issues regarding her sexual activity and views on reproduction with her doctor but also with her parent(s). In addition, a minor is exposed to Accutane counseling on contraception<sup>218</sup> that may be offensive to the patient or her parent(s). Such provisions can limit or deter access to the medication at a time in life when its psychological and social benefits are likely most acute. Furthermore, many state laws allow minors to receive sexual health treatment without parental consent, so the iPLEDGE provisions may pose a problem in requiring parents or guardians to sign consent forms authorizing acne treatment, which include the disclosure of use of contraception.<sup>219</sup>

### iii. Overall Social Cost of iPLEDGE

The program's effect on women of reproductive age takes a backward step in public policy, treating women based on their *potential* to become pregnant. The FDA clearly seeks to further the laudable goal of protecting future life. While this argument has been used in employment cases where environmental exposure effects women's reproductive organs, Accutane exposure is harmful to a fetus.<sup>220</sup> As a result, the FDA's goal in limiting treatment for women of child-bearing age implies that women and their doctors cannot make decisions regarding reproduction and sexual health without the involvement of a third party, the iPLEDGE program. This assumption interferes with the traditional patient-physician decision-making relationship, diminishes a woman's choice, and creates a potential for abuse by the manufacturer.

Consequently, the goal of the program's existence, to keep an effective acne treatment on the market,<sup>221</sup> is lost when patients who could benefit from its use do not have access to it. The social expense of iPLEDGE described above highlights the cost of interfering with personal autonomy. Another problem with the iPLEDGE program is limiting a patient's access to medication, which creates the

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<sup>217</sup> Center for Drug Evaluation and Research, *supra* note 127, at 36, 39.

<sup>218</sup> *Id.* at 20–21, 25, 38–39.

<sup>219</sup> See Rachel K. Jones, *Confidential Reproductive Health Services for Minors: The Potential Impact of Mandated Parental Involvement for Contraception*, 36 PERSP. ON SEXUAL & REPROD. HEALTH 182, 186–87 (2004).

<sup>220</sup> Center for Drug Evaluation and Research, *supra* note 127, at 11–12, 51–54.

<sup>221</sup> See Marilyn R. Pitts, FDA Safety Evaluator, Presentation at the American Society of Health-System Pharmacists Clinical Midyear (Dec. 7, 2005), *available at* <http://www.ashp.org/emplibrary/RiskManagementPlans.pdf>.

potential for abuse and subsequently unsafe use of medication. The next section illustrates how possibilities of abuse or noncompliance create safety concerns that outweigh the effectiveness of the Accutane.

*B. The Safety Cost: Weighing the Risks and Benefits of Accutane*

Congress requires the FDA to consider safety before it approves a new drug for market introduction.<sup>222</sup> A manufacturer must demonstrate safety with sufficient evidence when submitting a New Drug Application.<sup>223</sup> While Accutane was approved by the FDA as safe and effective in 1982, post-marketing analysis of the risk of pregnancy exposure to the drug prompted the introduction of a risk management program as a condition of keeping the medication on the market. Unfortunately, neither past programs nor iPLEDGE have or will eliminate pregnancy exposures. Therefore, the safety cost of Accutane being available on the market is too great to justify its benefit as an effective acne treatment.

The FDA bases pre-market approval of an NDA on a risk-benefit analysis “for the intended population and use.”<sup>224</sup> The importance of considering the intended population with the side effects of a medication is to assess the rate of risk. For example, Thalomid (thalidomide) and Tracleer, which both cause severe birth defects in pregnant patients, are prescribed to a much narrower patient population than Accutane.<sup>225</sup> Therefore the ability for this risk management program to be effective is decreased when there is a broader patient

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<sup>222</sup> 21 U.S.C.A. § 355(d) (West 2006). The term safe refers to “health of man or animal.” 21 U.S.C.A. § 321 (West 2006) (“Safe” was intended to include only the inherent safety of drug when used in the manner intended.).

<sup>223</sup> 21 U.S.C.A. § 355.

<sup>224</sup> FDA, Managing the Risks From Medical Product Use: Creating A Risk Management Framework at 21, <http://www.fda.gov/oc/tfrm/riskmanagement.pdf> (last visited Jan. 3, 2007) [hereinafter *Managing the Risks*].

<sup>225</sup> See Celgene, Thalomid, *supra* note 140; Tracleer, *supra* note 140. Thalomid treats multiple myeloma and severe erythema nodosum leprosum while Tracleer treats pulmonary arterial hypertension. See Celgene, Thalomid, *supra* note 140; Tracleer, *supra* note 140. These conditions occur in patient populations that are generally focused on fewer patients and older patients than Accutane’s intended population—adolescents and adults with severe forms of acne. See Celgene, Thalomid, *supra* note 140; Tracleer, *supra* note 140. The risk of pregnancy in pre-menopausal, sexually active patients creates a greater risk than in patient populations with that are postmenopausal, immunocompromised and physically impaired by their health condition, as is generally the situation with patients being treated with Thalomid and Tracleer. See Celgene, Thalomid, *supra* note 140; Tracleer, *supra* note 140. Also, neither Thalomid nor Tracleer is available in generic forms, thereby economically limiting patients from access to these therapies as well. See Celgene, Thalomid, *supra* note 140; Tracleer, *supra* note 140.

population within the age range to become pregnant using the medication. Thalomid and Tracleer have a greater potential to meet the FDA's zero pregnancy threshold goal since the number of patients being treated with the medication are less likely to be as sexually active or able to conceive compared to Accutane patients.<sup>226</sup> Thus, the Thalomid and Tracleer risk management programs have the ability to manage the risk of birth defects, while iPLEDGE has a much harder task.

The Agency acknowledges a safe product as one with "reasonable risks, given the magnitude of the benefit expected and the alternatives available."<sup>227</sup> However, no drug is without side effects.<sup>228</sup> The amount of risk acceptable in light of a drug's beneficial effect remains difficult to calculate.<sup>229</sup> Clinical trials can establish scientific data to illustrate whether a product is safe but such data does not conclusively suggest the value judgment that ultimately must be made as to the safety of a drug.<sup>230</sup> "[S]cience alone can never be an adequate basis for a risk decision . . . risk decisions are, ultimately, public policy choices."<sup>231</sup>

Keeping a beneficial medication available to patients by managing its side effects is good public policy. However, the ability to manage the side effects is key for this analysis. Risk assessment in pharmaceuticals involves the evaluation and analysis of risks associated with a drug product.<sup>232</sup> Most risk management programs encompass the following key components: identification of the problem, analysis

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<sup>226</sup> See Celgene, Thalomid, *supra* note 140; Tracleer, *supra* note 140.

<sup>227</sup> See Managing the Risks, *supra* note 224, at 3.

<sup>228</sup> See Celgene, Thalomid, *supra* note 140; Tracleer, *supra* note 140. "Although medical products are required to be safe, safety does not mean zero risk, since all medical products are associated with risks." Managing the Risks, *supra* note 224, at 3.

<sup>229</sup> In unsuccessful legislation, the FDA sought to define the term safe; "the term 'safe' means that the health benefits of the drug entity clearly outweigh the risks presented by the drug entity, taking into account the standards and requirements applicable to drug products . . ." James T. O'Reilly, 1 FOOD AND DRUG ADMIN. §14:4, n.14 (quoting S. 1045, 96th Cong. (1979); S. 2755, 95th Cong. §109(E) (1978)).

<sup>230</sup> See Managing the Risks, *supra* note 224.

<sup>231</sup> NATIONAL RESEARCH COUNCIL, UNDERSTANDING RISK: INFORMING DECISIONS IN A DEMOCRATIC SOCIETY 26 (1996).

<sup>232</sup> FETTERMAN, *supra* note 1, at 116.

Risk Assessment: as it relates to healthcare, scientific evaluation of known or potential adverse health effects resulting from human exposure to medication therapies.

Risk management: the systematic approach to setting the best course of action, policies, processes, procedures, practices, and resources to the assessment, communication and control of risk issues affecting human health and safety.

*Id.*

of the probability and severity of the risk, planning and communicating to control the risk, and evaluating the outcomes of interventions.<sup>233</sup>

The early stages of Accutane use in clinical trials illustrate the start of a public policy debate over whether the benefits of a miraculous acne treatment outweigh the drug's risk in causing fetal deformities. In the beginning, Accutane's benefits outweighed its known risk in pregnancy exposure.<sup>234</sup> No other medication on the market cured this degree of acne like Accutane.<sup>235</sup> In addition, the FDA never identified Accutane's devastating effect in human pregnancy during the pre-market approval phase.<sup>236</sup>

Not until post-marketing studies and voluntary patient reporting did the FDA identify human birth defects as an unacceptable risk of Accutane use.<sup>237</sup> Lack of complete data impaired the FDA's full assessment of the problem.<sup>238</sup> As a result, the Agency and manufacturer delayed implementing risk controls in order to understand where to attack the problem of exposure in pregnancy.<sup>239</sup> After gathering data and observing case reports of babies born with abnormalities, the FDA conditioned Accutane's continued sales on a zero pregnancy exposure policy.<sup>240</sup> The FDA would not compromise with Roche during the pre-S.M.A.R.T. time period to set a threshold limit on pregnancy exposure, apparently in conformity with the Agency's policy against harming future life.<sup>241</sup>

Nonetheless, even with the implementation of the S.M.A.R.T. program, pregnancies still occurred as a result of noncompliance in the broad patient population being treated with the medication.<sup>242</sup> This led to discussions regarding the creation of iPLEDGE.<sup>243</sup> With the approval of iPLEDGE the FDA pronounces that Accutane can be used safely, but only under restrictive distribution.<sup>244</sup> The FDA has

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<sup>233</sup> *Id.* at 68–69.

<sup>234</sup> See Background of Isotretinoin, *supra* note 17, at 1.

<sup>235</sup> *Id.* Accutane has been referred to as a “miracle drug” for its effectiveness in the treatment of severe acne. See *Issues Related to the Safety of Accutane*, *supra* note 33 (statement by Dr. Diana S. Berson, Associate Director of Dermatology at Cornell University).

<sup>236</sup> Riepenhoff & Somerson, *supra* note 37.

<sup>237</sup> See *id.*

<sup>238</sup> See *id.*

<sup>239</sup> See *id.*

<sup>240</sup> See Wilkin, *supra* note 95.

<sup>241</sup> *Id.*

<sup>242</sup> Mitchell et al., *supra* note 59, at 101–06; Leach, *supra* note 17.

<sup>243</sup> Center for Drug Evaluation and Research, *supra* note 127.

<sup>244</sup> See 21 C.F.R. § 314.520 (2000).

not attained its goal of zero pregnancy exposures, and fails to acknowledge the impossibility of obtaining complete patient adherence to any risk management program. Since physicians may legally prescribe drugs for off-label uses, it is not possible to ensure physician compliance to limit prescriptions only to the most severe acne cases. While a deviation from the program could invoke regulatory sanctions and other actions, punishing a pregnant woman for conceiving under iPLEDGE is harsh and impractical.<sup>245</sup>

While well-intentioned, the FDA is compromising public health. If past risk management programs were not successful in preventing exposed pregnancies, the use of a mandatory registry will not stop those patients too embarrassed to report their diversions to iPLEDGE from defying the program's mandates. The restrictive provisions of the program will not just deter women from taking the medication but may encourage the program's failure. Women of reproductive age who are sexually active may lie in their responses to the iPLEDGE database. Minors may feel great pressure to be dishonest in discussions with their parents or guardians, fail to reveal they are sexually active, and begin medication without any contraception. This increases the chance of an Accutane-exposed pregnancy.

Exposed pregnancies are inevitable with a medication treating a broad patient population, suggesting that the safe use of the isotretinoin is impossible. The FDA is simply attempting to avoid this immutable reality by affirming a third-generation risk management program for isotretinoin. Allowing a woman to face the horrible choice of having an unwanted abortion or a child with birth deformities due to drug exposure outweighs the need for clear skin even in the most severe cases of acne.

### III. CONCLUSION

The FDA's unwillingness to protect future life by taking Accutane off the market (a true zero tolerance of pregnancy rates) has simply gone on too long. As long as Accutane remains on the market, the goal of eliminating all fetal exposures will never be attained.<sup>246</sup> And yet, in pursuit of this flawed goal, iPLEDGE improperly limits women's autonomy through intrusive and ineffective

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<sup>245</sup> Center for Drug Evaluation and Research, *supra* note 127, at 38–39. As the U.S. News and World Report commented, “[a]n irresponsible pregnancy, once just a source of shame, will soon be a recordable national offense—that is if it occurs while taking the acne drug Accutane.” Bernadine Healy, *Pledging for Accutane*, U.S. NEWS & WORLD REP., Sept. 5, 2005, at 63.

<sup>246</sup> See Pitts, *supra* note 221.

provisions that are so strict that they actually encourage noncompliance.<sup>247</sup> The result of nonadherence is pregnancy exposure and the possibility of regulatory action punishing the patient. Instead of simply withdrawing the medication, the FDA limits the choice of a woman based on her potential to become pregnant in the hopes that this will eliminate pregnancy exposures.

The FDA's indecision incurs social and safety costs. Yet, the FDA has chosen to allow Accutane to remain on the market since 1982 with evidence of continued pregnancy exposures and birth defects in children. Dr. David J. Graham of the FDA stated, "Isotretinoin is one of five dangerous drugs that should be removed from the market."<sup>248</sup> The FDA, upon due notice to the manufacturer, has the statutory authority to immediately withdraw a product from the market by revoking the product's NDA on the grounds that the drug is an "imminent hazard" to the public health.<sup>249</sup> The FDA chooses iPLEDGE as the solution instead of making a tough decision regarding the value of preventing fetal exposure to Accutane. As a result, iPLEDGE "will bring guilt, lies, and misdemeanors but no fewer pregnancies or consequent abortions."<sup>250</sup> The FDA should take action and remove Accutane from the market before further pregnancy exposures occur.

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<sup>247</sup> Center for Drug Evaluation and Research, *supra* note 127.

<sup>248</sup> See Issues Related to the Safety of Accutane, *supra* note 33 (statement by Dr. David J. Graham of the FDA).

<sup>249</sup> O'REILLY, *supra* note 229, at §13:23. The Agency can also remove the drug from the market if:

1. The drug has been found unsafe under its labeled conditions of use, upon experience, tests or other scientific data
2. New evidence shows that the drug is not safe for its intended and labeled use
3. New information shows a lack of substantial evidence of effectiveness
4. The approved application is found to have an untrue statement of a material fact.

*Id.*

<sup>250</sup> Healy, *supra* note 245, at 63.