

## I. INTRODUCTION

Dealing with acne is no longer merely a rite of passage from adolescence to adulthood. Acne treatment and prevention have become issues that adults deal with as well.<sup>1</sup> There are more over-the-counter and prescription acne treatments available for acne sufferers. The days of using toothpaste and lemon juice as acne treatments have given way to a billion dollar business full of targeted marketing campaigns and significant monetary investment by drug companies. In fact, the market for prescription acne medications rose 16 percent, to \$1.1 billion in 2000, and 21 percent from 1998 to 1999, to \$960 million, according to IMS health, which tracks sales of prescription medication.<sup>2</sup> As for over-the-counter treatments, department store sales of acne remedies rose 73 percent in 1999 and 45 percent in 2000, to \$22 million.<sup>3</sup>

Drug companies are generally using the media to promote their products to reach their targeted consumer base: teenagers and other sufferers of acne. Roche and Galderama, two large pharmaceutical companies, have been running ad campaigns specifically aimed at teenagers to make them aware of prescription medications that treat acne.<sup>4</sup> One Roche commercial features a teenager suffering from acne who is called “pizza face” by other students. This commercial is a “health education message” that talks about acne but does not explicitly mention any prescription acne drug. Hemnan Shah, a pharmaceutical consultant, sees the value for Roche and similar pharmaceutical companies in using this type of marketing strategy. He states that the strategy makes sense because if more patients (and potential consumers) go consult their doctor or a dermatologist for acne, a certain percentage will be prescribed the most popular prescription acne medication

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<sup>1</sup> “In fact, doctors say, female adults are seeking treatments much more often than in the past, raising sales of everything from body washes to birth control pills in their quest for clear skin.” Julian Barnes, *A New Age in Acne Treatment; It's No Longer Just a Market for Teenagers*, N.Y. TIMES, April 27, 2001 at C-1.

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

<sup>3</sup> *Id.*

<sup>4</sup> *Teenagers have Largely Escaped Prescription Medicine Promotional Campaigns, Until Now*, Patricia Winters Lauro, N.Y. TIMES, March 16, 2000, at C-14.

on the market – Roche’s Accutane.<sup>5</sup>

This investment in marketing makes sense when one considers how large the market for Accutane and other prescription acne medication has become. In 2000, sales of Accutane reached \$587 million, up 21 percent from 1999.<sup>6</sup> This increase in sales has occurred despite the fact that it is known to cause birth defects in pregnant women and the fact that it has recently been linked to depression and in some cases, severe depression leading to suicide. The overall increase in sales may indicate that Accutane is being used to treat conditions other than the most disfiguring types of acne. In fact, many dermatologists are increasingly prescribing Accutane as a routine acne treatment despite the fact that it is labeled as being intended for only the most severe forms of cystic acne. A survey of over 600 dermatologists in the United States found that doctors were prescribing isotretinoin, the active ingredient in Accutane, for indications other than those contained in the official labeling.<sup>7</sup> Between 1993 and 2000, the proportion of isotretinoin treatment for severe acne declined from 63% to 46%, whereas the proportion of treatment for mild to moderate acne increased from 31% to 49%.<sup>8</sup>

There are increasing numbers of teenagers using Accutane as well. Much of this increased use, by both teenagers and those with mild to moderate acne, can be attributed to an increased number of advertisements on TV and in well-known fashion and teen magazines.<sup>9</sup> One reason for this is that Hoffman-La Roche, the manufacturer of Accutane, took strategic steps to grow brand recognition through the use of television,

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<sup>5</sup>*Id.*

<sup>6</sup>Barnes, *supra* note 1.

<sup>7</sup>*Issues Relating to the Safety of Accutane: Hearing Before the Subcomm. On Oversight and Investigations of the House Committee on Energy and Commerce, 108<sup>th</sup> Cong.* (December 11, 2002)(testimony of Lynn Martinez, Director of Teratology and Birth Defects Program, Utah Department of Health).

<sup>8</sup>Diane K. Wysowski, Joslyn Swann, & Amarilys Vega, *Use of Isotretinoin (Accutane) in the United States: Rapid Increase from 1992 through 2000*, Office of Post-Marketing Drug Risk Assessment, Food and Drug Administration (September 17, 2001).

<sup>9</sup>Ellen Rafshoon, *What Price Beauty?*, BOSTON GLOBE MAG., April 27, 2003. Accutane has also become known as a “wonder drug” in Hollywood circles. Many of the stars that teenagers watch on television or in the movies may be achieving their flawless complexions through using Accutane for mild acne and other skin related imperfections. Ava Shamban, the director of the Laser Institute for Dermatology and European Skin Care in Santa Monica, California has said, “But it’s [Accutane] still a quick fix if an actress has an upcoming role because the surface acne clears in a matter of weeks. Accutane is so popular in Hollywood because it’s just so effective.” *Issues Relating to the Safety of Accutane: Hearing Before the Subcomm. On Oversight and Investigations of the House Committee on Energy and Commerce, 108<sup>th</sup> Cong.* (December 11, 2002)(Exhibit - “Small Wonder,” Elle Magazine article)

print, and internet media.<sup>10</sup> Teenagers were specifically targeted in an effort to increase market share.<sup>11</sup> The 2001 Roche Accutane marketing strategic plan even specifically targets teenage males stating, “The acne awareness DTC (direct to consumer) targets the teen male audience and their moms, because young men suffer from more severe acne, with a longer duration, than their female counterparts, and their moms because they are the key decision makers in the household. In addition, *males are less likely to seek medical treatment than their female counterparts.* (italics added)”<sup>12</sup> This emphasis on advertising and extreme attention to detail regarding targeted marketing has increased market share so drastically that Accutane really has no other major competitors among other prescription anti-acne drugs.<sup>13</sup>

The risks of Accutane use are more pronounced now than ever because of the growing popularity of this drug as an acne fighting “wonder drug.” From 1992 to 2000, there was a 250% increase in the number of dispensed prescriptions for isotretinoin in the United States.<sup>14</sup> A generic form of Accutane has also recently been approved for marketing in the United States.<sup>15</sup> The FDA approved the first generic version of isotretinoin, *Amnesteem*, on November 8, 2002.<sup>16</sup> This development, coupled with the increasing use of Accutane for even mild forms of acne, indicates that Accutane prescription and use will continue to increase. Along with this increase in use will come an increase in the number of individuals potentially exposed to the serious health risks associated with Accutane.

This paper begins by examining the history, efficacy, and controversy surrounding the use of Accutane as an acne treatment. The next part of this paper examines the ways the FDA and Roche itself have attempted to

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<sup>10</sup> *Issues Relating to the Safety of Accutane: Hearing Before the Subcomm. On Oversight and Investigations of the House Committee on Energy and Commerce, 108<sup>th</sup> Cong.* (December 11, 2002)(Exhibit – “Roche 2001 Strategic Plan for Accutane,” Roche Laboratories).

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

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

<sup>13</sup> *See id.*

<sup>14</sup> Wysowski, *supra* note 8.

<sup>15</sup> Martinez, *supra* note 7.

<sup>16</sup> *Issues Relating to the Safety of Accutane: Hearing Before the Subcomm. On Oversight and Investigations of the House Committee on Energy and Commerce, 108<sup>th</sup> Cong.* (December 11, 2002)(testimony of Janet Woodcock, Center for Drug Evaluation and Research). “This generic product will be marketed by Bertek Pharmaceuticals of Research Triangle Park, NC, the branded arm of Mylan Laboratories. All generic brands of isotretinoin will utilize the labeling that is alike in all material respects to the name brand, educational tools, distribution requirements, and follow-up metrics in place under S.M.A.R.T.” *Id.*

regulate against the dangerous side effects of Accutane and the litigation that has resulted from past failure to adequately address these side effects. The conclusion of this paper examines the lessons learned from the past history of Accutane regulation as a starting point for continued reform to ensure that an effective drug remains available to consumers while properly warning of dangerous and potentially life-threatening side effects.

## II. WHAT IS ACNE AND HOW DOES ACCUTANE WORK?

Acne is a common skin disorder that usually occurs in adolescence, but is increasingly becoming an issue for adults as well. Essentially, acne occurs when hair follicles and the sebaceous glands inside the follicles become inflamed. When inflamed, these glands produce an oil substance called sebum that leads to bacterial growth and clogging of the follicles.<sup>17</sup> Dead cells inside hair follicles normally are shed and come out on the surface of the skin. But in people with acne, these cells shed faster, stick together, mix with sebum, and then clog the follicle.<sup>18</sup> Then bacteria contaminates the skin cell and sebum. As this bacteria grows, the body's immune system attempts to destroy it and inflammation results.

Accutane, a derivative of vitamin A, helps the function of the follicles return to normal, lowering the production of the sebum, slowing the growth of bacterium, and reducing inflammation.<sup>19</sup> This drug is somewhat unique among similar drugs because of its ability to affect all primary underlying causes of acne formation.<sup>20</sup>

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<sup>17</sup>United States Food and Drug Administration, *Why Acne Forms and How Accutane Knocks It Out*, FDA CONSUMER MAG., (March-April 2001).

<sup>18</sup>*Id.*

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

<sup>20</sup>*Id.*

One course of Accutane treatments, lasting typically about five months, results in prolonged remission of acne in up to 85 percent of patients.<sup>21</sup> However, Accutane is normally reserved for cases of “severe recalcitrant nodular acne,” according to its labeling.<sup>22</sup> This type of acne is normally resistant to standard acne treatments, both over-the-counter and prescription antibiotics.<sup>23</sup> It is characterized by many nodules or cysts, which are inflammatory lesions filled with pus and lodged deep under the skin.<sup>24</sup> Accutane is especially effective in treating this type of potentially disfiguring acne (due to scarring).<sup>25</sup> In this type of situation, Accutane is typically used after patients have failed topical and systemic antibiotic treatments and have no other therapeutic options.<sup>26</sup> Over 80 percent of patients require only one 4-5 month course of treatment to eliminate the Severe Recalcitrant Nodular Acne and avoid disfiguring scars.<sup>27</sup>

### III. THE HISTORY OF ACCUTANE

#### Overview of New Drug Approval Process

Before a new drug can be tested in humans, the manufacturer must carry out a variety of tests on laboratory animals.<sup>28</sup> Many of these tests address the toxicity or other potential dangerous side effects of the drug that

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<sup>21</sup>Michelle Meadows, *The Power of Accutane: The Benefits and Risks of a Breakthrough Acne Drug*, FDA CONSUMER MAG., (March-April 2001), available at [http://www.fda.gov/fdac/features/2001/201\\_acne.html](http://www.fda.gov/fdac/features/2001/201_acne.html).

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

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

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

<sup>25</sup>*Issues Relating to the Safety of Accutane: Hearing Before the Subcomm. On Oversight and Investigations of the House Committee on Energy and Commerce, 108<sup>th</sup> Cong.* (December 11, 2002)(testimony of George B. Abercrombie, President and Chief Executive Officer of Hoffman-La Roche, Inc.).

<sup>26</sup>*Id.*

<sup>27</sup>*Id.*

<sup>28</sup>Joan H. Krause, *Accutane: Has Drug Regulation in the United States Reached Its Limits?*, 6 J. L. & HEALTH 5 (1991-92).

is being tested.<sup>29</sup> Once animal testing is completed, the manufacturer must then submit the results to the FDA, along with detailed descriptions of proposed human studies in the form of an “investigational new drug (IND) application.”<sup>30</sup> The IND process includes reviews by clinical research experts of the Center for Drug Evaluation and Research, meetings between the FDA and the drug developer, tests, and the development of safety data.<sup>31</sup> Then the drug becomes involved in a series of clinical studies as the interactions between the FDA and the drug developer continue.

At this point, three distinct stages of clinical testing begin. In Phase I, trials are conducted primarily with the safety of the drug in mind.<sup>32</sup> In Phase II, trials are commenced to study the efficacy of the drug for its intended purpose.<sup>33</sup> Phase II trials involve significantly larger numbers of human subjects and may also uncover short-term side effects in certain targeted patient populations.<sup>34</sup> Phase III trials may involve several thousand patients with the indicated disease and may last four years or more.<sup>35</sup> This last set of trials is intended to discover more obscure side effects and also to approximate normal medical usage of the drug.<sup>36</sup> These Phase III tests address both effectiveness and safety, with these observations forming the basis for risk assessments and label warnings.<sup>37</sup> Once this stage is complete, the sponsor files a “New Drug Application (NDA).”<sup>38</sup> Final approval of the drug for marketing then turns on whether the manufacturer has proved the drug is safe and effective and whether the labeling for the product is accurate and easy for consumers to understand.<sup>39</sup>

Throughout this process, the FDA is actively involved at every stage. The Center for Drug Evaluation

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

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

<sup>31</sup> JAMES T. O'REILLY, FOOD AND DRUG ADMINISTRATION, §13-64 (1995).

<sup>32</sup> Krause, *supra* note 28.

<sup>33</sup> *Id.*

<sup>34</sup> *Id.*

<sup>35</sup> O'REILLY, *supra* note 31 at §13-66.

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

<sup>37</sup> *Id.*

<sup>38</sup> Krause, *supra* note 28, at 6.

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

and Research completes several reviews of the NDA.<sup>40</sup> An advisory committee to the FDA may also review the new drug and advise what additional work still needs to be done.<sup>41</sup> Even after approval, the FDA has several controls in place. For one, the FDA requires that the first advertisements for a prescription drug be submitted to the FDA and thereafter, the FDA can request submission at essentially any time.<sup>42</sup> Additionally, as will be discussed later in this paper, there is a process by which adverse reactions to the drug can be reported.<sup>43</sup> During the first year of approval, these adverse reactions must be submitted very rapidly to the FDA.<sup>44</sup> Lastly, the FDA continues to maintain and examine data on the efficacy and safety of the newly approved drug.<sup>45</sup>

## The Approval of Accutane in the United States

Accutane was developed as a treatment for severe forms of acne in Switzerland in the 1950's.<sup>46</sup> However, it was apparent immediately that the use of this drug could cause birth defects in pregnant women. This awareness of the teratogenic effects of Accutane prevented the use and marketing of this drug for two decades.<sup>47</sup> One reason for this caution was the Thalidomide tragedy in Europe that took place in the early 1960's. Thalidomide was a tranquilizer that was marketed as a sedative and a morning sickness remedy. In the early 1960's, it became clear that Thalidomide use had caused thousands of grotesque deformities in thousands of European babies, ultimately leading to a rethinking of drug regulation in both Europe and the United

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<sup>40</sup> See O'REILLY, *supra* note 31 at §13-64.

<sup>41</sup> *Id.* at §13-67.

<sup>42</sup> *Id.* at §13-69.

<sup>43</sup> *Id.* at §13-70, §13-71.

<sup>44</sup> *Id.* at §13-70.

<sup>45</sup> See *Id.* at §13, 69-74.

<sup>46</sup> Krause, *supra* note 28, at 7.

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

States.<sup>48</sup>

It was not until the late 1970's that Hoffman-LaRoche began testing Accutane for use in treating severe recalcitrant cystic acne.<sup>49</sup> Because of the drug's teratogenic properties, most test centers excluded women from the original human trials.<sup>50</sup> In fact, Accutane was tested in only 550 individuals before receiving approval from the Food and Drug Administration.<sup>51</sup> In May 1982, the U.S. became the first country to approve Accutane for use in the treatment of severe recalcitrant acne.<sup>52</sup>

By 1983, Roche became aware of at least three cases of malformed children born to women who were taking Accutane.<sup>53</sup> At that time, the original package insert for Accutane contained general warnings against use by pregnant women but only noted that the drug caused birth defects in animal trials.<sup>54</sup> Public Citizen, a consumer advocacy group, began to petition the FDA for warning labels regarding Accutane's risk of birth defects and other side effects.<sup>55</sup> Later in that year, the FDA began to receive an increased number of reports of "adverse pregnancy outcomes" resulting from Accutane use.<sup>56</sup> Roche began to communicate concerns about these outcomes through "Dear Doctor" letters sent directly to physicians.<sup>57</sup> Soon thereafter, Roche revised the labeling of Accutane to provide information about human birth defects.<sup>58</sup>

Despite this change in labeling, by 1984, 21 cases of Accutane-associated birth defects and 24 spontaneous

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<sup>48</sup> *Id.* at 4. The Thalidomide tragedy in Europe convinced Congress to require that new drugs be proven both safe *and* effective for their intended uses. A detailed system for drug approval was created, which included requirements for both animal studies and human clinical trials. *Id.* at 4-5. "Congress enacted the Drug amendments of 1962 hurriedly in the crisis atmosphere of the Thalidomide tragedy. In addition to requiring that FDA affirmatively determine that new agents have been demonstrated by "substantial evidence" to be effective, as well as shown to be safe, the Amendments required FDA to review all NDAs that had become effective during the previous twenty-four years to determine whether the products met the new effectiveness standard. . . President Kennedy signed the Amendments into law on October 6, 1962, 76 Stat. 780." PETER BARTON HUTT & RICHARD A. MERRILL, FOOD AND DRUG LAW: CASES AND MATERIALS 478 (1991).

<sup>49</sup> Krause, *supra* note 28, at 7.

<sup>50</sup> *Id.*

<sup>51</sup> *Id.* In fact, FDA approval of Accutane was unusually quick, coming only 9 months after the submission of the new drug application by Hoffman-LaRoche. *Id.*

<sup>52</sup> *Id.*

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

<sup>54</sup> *Id.*

<sup>55</sup> "Accutane: Chronology," from the Homepage of Congressman Bart Stupak, *available at* <http://www.house.gov/stupak/accutane-chronology.htm>.

<sup>56</sup> Krause, *supra* note 28, at 7.

<sup>57</sup> *Id.*

<sup>58</sup> *Id.* at 8.

abortions had been reported to the FDA.<sup>59</sup> As a result, Accutane’s warnings about birth defects were strengthened considerably. These warnings included suggestions to use contraception for a month before and after therapy, to participate in pregnancy tests before commencing therapy, and advising that blood banks avoid donors exposed to Accutane treatments.<sup>60</sup> Roche also made efforts to publicize the risks of Accutane to both potential patients and to prescribing physicians.<sup>61</sup> One way that Roche attempted to increase the information available to patients was to amend Accutane’s package insert. This package insert was changed once in 1985 and again in 1986 to reflect the potential dangerous side effects associated with Accutane use.<sup>62</sup>

However, by April 1988, the FDA had concluded that the education and warnings regarding birth defects resulting from Accutane use had not been effective.<sup>63</sup> Consequently, the FDA required significant changes including informed consent forms, large-sized boxed contraindications section, the use of “Pregnancy Prevention Kits,” and more detailed packaging.<sup>64</sup> The FDA also required additional studies, including follow-up patient surveys.<sup>65</sup> At the same time, in an effort to ensure that Accutane would still be widely available to consumers, the FDA disregarded an advisory committee recommendation to restrict prescribing of Accutane to board-certified dermatologists.<sup>66</sup> This tension between availability and overall safety was exacerbated by a 1990 FDA memo that concluded, “the magnitude of injury and death has been great and permanent, with 11,000 to 13,000 Accutane related abortions and 900 to 1,100 Accutane-related birth defects.”<sup>67</sup>

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<sup>59</sup> *Id.*

<sup>60</sup> *Id.*

<sup>61</sup> *Id.*

<sup>62</sup> In June of 1985, Roche amended the package insert under “Adverse Reactions” to state: “The following CNS reactions have been reported and may bear no relationship to therapy – seizures, emotional instability including depression, dizziness, nervousness, drowsiness, malaise, weakness, insomnia, lethargy and paresthesias.” In August of 1986, Roche further amended this package insert to state: “Depression has been reported in some patients on Accutane therapy. In some of these patients, this has subsided with discontinuation and recurred with reinstatement of therapy. “Accutane: Chronology” Web Page of Congressman Bart Stupak.

<sup>63</sup> Krause, *supra* note 28, at 8.

<sup>64</sup> *Id.* at 9.

<sup>65</sup> *Supra* note 55.

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

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

In 1996, the FDA required a Medication Guide program that provided patients with drug information leaflets known as “patient package inserts” (PPI).<sup>68</sup> This program included drugs with serious side effects, including Accutane.<sup>69</sup> These PPI guides must be distributed by the pharmacist to patients each time an Accutane prescription is dispensed.<sup>70</sup> These guides summarize information on key safety issues regarding the use and treatment of Accutane.<sup>71</sup>

In the late 1990’s, the tension between the manufacturer of Accutane, Roche, and the FDA increased due to a number of conflicts. In March of 1997, French health authorities required Roche to add “suicide attempt” to Accutane’s published side effects based on a two-year study of Accutane’s connection with depression.<sup>72</sup> Roche did not inform the FDA of this development.<sup>73</sup> In August 1997, the FDA issued a warning letter to Roche for failing to submit serious adverse events reports in a timely manner.<sup>74</sup> A February 1998 FDA memo concluded that Roche “had not acted in good faith to truly and accurately answer questions relating to Accutane use in women and pregnancy exposure.”<sup>75</sup> The FDA memo also asserted that “Given all the pieces of evidence available, it is difficult to avoid the conclusion that Accutane can adversely affect the adult human brain in clinically significant ways and that Accutane use is associated with severe psychiatric disease in some patients.”<sup>76</sup> As a result, FDA required Roche to add a new warning to Accutane’s physician package insert and Roche began to independently increase efforts at patient education.<sup>77</sup>

Roche also began to conflict with the FDA in regard to Accutane advertising. The FDA requested in a March 5, 1998 warning letter that Roche cease “dissemination of all materials and claims that state, suggest, or

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<sup>68</sup> *Id.*

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

<sup>70</sup> Woodcock, *supra* note 16.

<sup>71</sup> *Id.*

<sup>72</sup> *Supra* note 55.

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

<sup>74</sup> *Id.*

<sup>75</sup> *Id.*

<sup>76</sup> *Id.*

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

imply that Accutane is safe and effective for psychological or emotional suffering, including depression. . . .”<sup>78</sup>. This letter emphasized “Roche’s failure to disclose important risk information in its promotional materials.”<sup>79</sup> Roche’s promotional materials stated that Accutane was both safe and effective in the treatment of what Roche described as the “psychosocial trauma” and “emotional suffering” associated with acne, including “negative psychosocial effects such as depression and poor self image.”<sup>80</sup> The FDA added that “this claim was particularly troublesome in light of information recently presented in a Dear Doctor letter that Accutane may cause depression, psychosis, and rarely, suicidal ideation, suicide attempts and suicide.”<sup>81</sup> Consequently, Roche changed the warnings on the package label to include: “. . . depression, and rarely suicidal thoughts, suicide attempts and suicide.”<sup>82</sup> This was the first time that the packaging of Accutane contained the full psychiatric warnings mentioning both depression and suicide.<sup>83</sup>

In September 2000, the FDA’s Dermatologic and Ophthalmic Drug Advisory Committee held a meeting on Accutane’s risks of birth defects and psychiatric disorders.<sup>84</sup> The FDA concluded that from 1982 to May 2000, Accutane was associated with 147 suicides and hospitalizations for depression.<sup>85</sup> There were now over 500 formal adverse reaction reports of suicide, suicide attempt and suicide ideation recorded by national and international health agencies for Roaccutane/Accutane.<sup>86</sup> Overall, Accutane still had the fourth highest record of adverse reaction reports in the United States.<sup>87</sup> Based upon these statistics, the Committee unanimously agreed that there was sufficient concern about Accutane to justify exploring additional risk management strategies even though the risk was uncertain.<sup>88</sup> The Committee recommended that Roche: 1)

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<sup>78</sup>Letter from the Department of Health and Human Services to Mr. Patrick J. Zenner, President and CEO of Hoffman-LaRoche, Inc. (March 5, 1998).

<sup>79</sup>*Id.*

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

<sup>81</sup>*Id.*

<sup>82</sup>*Supra* note 55.

<sup>83</sup>*Id.*

<sup>84</sup>*Id.*

<sup>85</sup>*Id.*

<sup>86</sup>“Label History/Label Warnings,” Accutane Action Group *available at* <http://www.accutaneaction.com>.

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

<sup>88</sup>*See Accutane – Is This Acne Drug Treatment Linked to Depression and Suicide: Hearing Before the House Comm. on*

add the information about the adverse events to the informed consent document signed by patients and/or their parents or guardians prior to receipt of Accutane; 2) develop and distribute an enhanced prescriber educational program about the psychiatric events; and 3) develop and distribute a new Medication Guide for Accutane.<sup>89</sup>

## Overview of “Labels” and “Labeling”

A drug label is the primary means to communicate instructions about proper use and also information about safety and potential dangerous side effects.<sup>90</sup> Information requirements for drug labels in package form include the name of the manufacturer, active ingredients, the established name of the drug, adequate directions for use, adequate warnings, and other information that is explicitly required by FDA regulations.<sup>91</sup> A label is insufficient to meet Food and Drug Administration requirements if it gives inadequate information or if it is affirmatively misleading through false statements or important omissions of necessary information. It is also important that this information is clearly visible and easily understandable not only to the physician and the pharmacist, but also to the patient.<sup>92</sup>

Deceptive label statements can be punished by the FDA through their misbranding authority.<sup>93</sup> For new drugs, the FDA screens out deceptive label claims through the new drug approval process.<sup>94</sup> The requirement

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*Committee on Government Reform*, 106<sup>th</sup> Cong 112 (December 5, 2000)(statement of Dr. Jonica Bull, Director of the Office of Drug Evaluation V of the Center for Drug Evaluation and Research).

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

<sup>90</sup>O'Reilly, *supra* note 31 at §15, 15-23.

<sup>91</sup>*Id.* at §15, 23-24.

<sup>92</sup>*See id.* at §15, 15-23. (“The 1938 Act did not set a specific requirement for display of certain information in certain places, but congressional intent was clear that ‘in the making up of labels and labeling the required material should not be hidden in the folds and recesses of the labels or stated in size type not readily readable.’”).

<sup>93</sup>*Id.* at §15- 25.

<sup>94</sup>*Id.*.

for accurate label claims is met by the FDA's parallel requirement for proof of efficacy, since an ineffective drug could not claim that it is effective without being misbranded.<sup>95</sup> Outside of the new drug approval process, in judging whether a drug label is misleading or not, the total context of the claim should be examined, including the appearance of the label.<sup>96</sup> The determination of whether a label is misleading or not is judged by the standard of clarity and understandability to the consumer, not the physician or the pharmacist.<sup>97</sup> There is a difference however, between the "label" and the "labeling" of a prescription drug, such as Accutane. The "label" is merely the outside package of the drug. "Labeling" is the set of communications that physically accompany the drug to the prescribing physician or to the consumer.<sup>98</sup> The FDA requires that the drug manufacturer appropriately and understandably communicate certain information to this physician or consumer.<sup>99</sup> If a drug label cannot carry all the information that the FDA requires, the agency may insist on labeling such as package inserts.<sup>100</sup> Labeling may include additional precautions, contraindications (who should not take the drug), information about harmful side effects, and any other information that the FDA may deem necessary.<sup>101</sup>

Claims made in labeling must follow the same standard used in considering the legality of prescription drug labels.<sup>102</sup> Labeling is deemed to be deceptive if it is false or misleading. The claims made by the manufacturer are held to a "high level of honesty" and an "exacting level of truthfulness."<sup>103</sup> With the recent increase in the amount of prescription drug advertising, these standards have become even more relevant. If material can be described as serving both an advertising function and a labeling function, it is subject to FDA jurisdiction as labeling since Congress did not intend to exclude accompanying information that

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<sup>95</sup> *Id.*

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

<sup>97</sup> *Id.*

<sup>98</sup> *Id.* at 26.

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

<sup>100</sup> *Id.*

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

<sup>102</sup> *Id.* at 27.

<sup>103</sup> *Id.*

promotes a pharmaceutical product's sale from labeling jurisdiction.<sup>104</sup> FDA regulation of labeling (and advertising) is especially relevant to Accutane and its manufacturer, Hoffman-La Roche, because it is an increasingly popular prescription drug that has also been linked to dangerous side effects that consumer must be made aware of.

## The Controversy Surrounding Accutane Labeling

The original Accutane labeling included only such side effects as severe drying and chapping of lips and elevated cholesterol levels.<sup>105</sup> This labeling referred to evidence of birth defects in animal trials but stated that there was no equivalent evidence in human trials.<sup>106</sup> This relatively lax concern about the caution necessary in labeling is exceedingly problematic concerning the general awareness of the danger of severe birth defects resulting from Accutane use. After all, upon development, this drug was delayed in production and marketing for this very reason.

In 1983, concerns began to be raised about the dangerous side effects of Accutane use. In July and August, the first "Dear Doctor" letters were sent out warning about potential side effects and the FDA published reports of the first 12 reported "adverse pregnancy outcomes" in the August 27, 1983 issue of the *Lancet*.<sup>107</sup> In September of 1983, the first changes were made to what was then a fairly standard label. The Accutane label was modified to include information about "human congenital abnormalities," and the pregnancy concern was put into boldface type.<sup>108</sup> This new label also included information about serious effects to both

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

<sup>105</sup> Krause, *supra* note 28, at 17.

<sup>106</sup> This statement was literally true since pregnant women were excluded from any clinical trials. *Id.*

<sup>107</sup> *Id.*

<sup>108</sup> *Id.*

the central nervous system and gastrointestinal side effects, reminding practitioners that the drug should be reserved for the most severe forms of recalcitrant cystic acne.<sup>109</sup>

In early 1984, the label for Accutane was again changed due to an increase in the number of spontaneous abortions and birth defects reported to the FDA.<sup>110</sup> Roche now advised women to use contraception for a month before and after Accutane use, requested a pregnancy test two weeks before the start of treatment, and added a boxed warning about a cerebral side-effect that mimicked the symptoms of a brain tumor.<sup>111</sup> Roche also prepared educational advertisements detailing proper prescribing procedures, which appeared in medical and pharmacy journals.<sup>112</sup> Over the next several years, only minor changes were made to Accutane's labeling despite a continuance of reports of birth defects and other dangerous side effects.

In 1988, the FDA began to face increased pressure to significantly restrict Accutane sales. Suggestions included limiting prescriptions to certain types of specialists, curtailing the availability of Accutane to doctors, limiting the types of patients who could obtain the drug (by age or form of acne), and requiring two medical opinions before providing a prescription for treatment.<sup>113</sup> One organization went a step further than even these suggestions. The Public Citizen Litigation Group soon filed a petition requesting that the FDA invoke imminent hazard provisions to remove Accutane from the market until highly restrictive new approval restrictions could be implemented.<sup>114</sup> The FDA began receiving suggestions that it either ban the drug or restrict Accutane prescriptions to dermatologists.<sup>115</sup> Although the FDA rejected an outright ban or overly stringent restrictions on prescription, purchase, or use, the FDA was facing increased public pressure to regulate Accutane in *some* way.

The FDA declined to restrict access to Accutane, instead choosing to make significant labeling changes.

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<sup>109</sup>*Id.* at 17-18.

<sup>110</sup>*Id.* at 18.

<sup>111</sup>*Id.*

<sup>112</sup>*Id.*

<sup>113</sup>*Id.* Although these recommendations were made, it was uncertain whether the FDA had the legal right to take such actions. The FDA had never taken such actions against an already approved drug. *Id.*

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

<sup>115</sup>*Id.*

Revised patient labeling included a statement that the risk of birth defects was one in four or greater, a photograph of an infant with typical Accutane-caused deformities, advice that patients obtain an informed consent form, a statement advising prescriptions to begin only on the second or third day of the menstrual cycle, and a phone number to call for additional information.<sup>116</sup> The revised physician labeling included stronger contraindications in larger print and advised that Accutane be withheld from the patient unless the patient is fully capable of both understanding the risks of use and complying with the procedures of treatment.<sup>117</sup>

For a number of years, the Accutane label remained relatively constant because it dealt merely with the issue of birth defects in pregnant women. But in the 1990's, Accutane began to be associated with the side effect of depression and suicidal ideation. Adverse reports began to come in to the FDA and the FDA and Roche began to talk about these concerns, discussing potential changes to the labeling among other precautionary measures. In 1998, the FDA required Roche to add a boldface warning of psychiatric disorders to Accutane's physician package insert.<sup>118</sup> In May 2000, the Accutane label includes warnings in boldface about "...depression, and rarely suicidal thoughts, suicide attempts, and suicide..."<sup>119</sup>

Interestingly, several other countries that have approved Accutane for use as an acne treatment included comprehensive warnings about the possible psychiatric side effects in Accutane labeling. These warnings were included at approximately the same time that the labeling was changed in the United States. A detailed study took place in France from 1992 to 1994 on the association of depression with Accutane (Roaccutane).<sup>120</sup>

In March of 1997, the French added "suicide attempt" to pre-existing warnings of behavioral difficulties, con-

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<sup>116</sup>*Id.* at 19.

<sup>117</sup>*Id.*

<sup>118</sup>"WARNINGS – Psychiatric Disorders: Accutane may cause depression, psychosis, and rarely suicidal ideation, suicide attempts, and suicide. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary. No mechanism of action has been established for these events." *Supra* note 86.

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

<sup>120</sup>*Id.* Roche did not originally inform the FDA about this French study or French changes in Accutane labeling. The FDA became aware that French authorities had already required the addition of an Accutane "suicide attempt" warning in 1997 or this study (or the failure to disclose this information) until July 1998. *Id.*

vulsions, and depressive symptoms.<sup>121</sup> The French had long been aware of the potential depressive effects of Accutane on certain users. In the United Kingdom, the Accutane warning on the labeling read, “Roaccutane may cause depression, psychotic symptoms, and, rarely suicide attempts and suicide. Particular care needs to be taken with patients with a history of depression and all patients should be monitored for signs of depression and be referred for appropriate treatment if necessary.”<sup>122</sup> The Canadian label warning was also very specific about the danger of suicide and depression.<sup>123</sup> Despite these recent changes in Accutane labeling to reflect greater concern about psychiatric side effects, Accutane often continues to be sold (in all these countries, including the United States) without inclusion of the increased label warnings, according to one advocacy group.<sup>124</sup>

## IV. ACCUTANE AND BIRTH DEFECTS

### The Link Between Accutane and Birth Defects

Over the past ten years, the estimated number of Accutane prescriptions for women who are capable of reproduction has more than doubled.<sup>125</sup> In fact, Accutane has quickly become the most widely used teratogenic drug in the United States.<sup>126</sup> It has been a known teratogen that can cause severe birth defects

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<sup>121</sup> *Id.*

<sup>122</sup> *Id.*

<sup>123</sup> *Id.* The label warning of April 2000 on the Patient Insert read, “Special Symptoms You Should Tell Your Doctor About: If you feel or become depressed, have thoughts of suicide, are unable to sleep and have mood swings while taking ‘Accutane,’ tell your doctor as soon as possible. These feelings, although they do not happen very often, may occur when you are taking ‘Accutane’ or after you have stopped taking ‘Accutane.’ It has not been established whether or not these symptoms may be related to ‘Accutane.’ However, it is important to tell your doctor as soon as possible, if you have feelings.” *Id.*

<sup>124</sup> *Id.*

<sup>125</sup> M.A. Honein, L.J. Paulozzi, and J.D. Erickson, *Continued Occurrence of Accutane-Exposed Pregnancies*, 59 *TERATOLOGY* 142-147 (2001). Reproductive aged women are from 15-44 years old. Such women account for approximately 90% of prescriptions for women overall. Overall, the estimated number of Accutane prescriptions has more than doubled from fewer than 750,000 prescriptions in 1989 to more than 1,800,000 prescriptions in 1999. *Id.*

<sup>126</sup> *Id.* “Accutane carries the notorious distinction of being the most widely prescribed birth defect-causing medicine in the

including cranio-facial, cardiac, thymic, and central nervous system malformations.<sup>127</sup>

Within a few years of Accutane's entry into the market in 1982, a team of genetics specialists studied the outcomes of more than a hundred Accutane exposed pregnancies.<sup>128</sup> They calculated a 35 percent chance of giving birth to a child with multiple major deformities.<sup>129</sup> But because Accutane is such a potent teratogen, crossing the placenta and affecting fetal development, an unusually high number of pregnant women using Accutane birth stillborn infants or miscarry.<sup>130</sup> Due to these concerns, many women who become pregnant while using Accutane choose to abort – approximately 61 percent of Accutane pregnancies are medically terminated.<sup>131</sup>

The reason why Accutane (isotretinoin) has these teratogenic effects is because it is a synthetic relative of Vitamin A<sup>132</sup>. Although Vitamin A is crucial for normal fetal growth and development, excessive consumption of Vitamin A can cause birth defects.<sup>133</sup> Several recent studies have emphasized this fact. A 1995 study found that women who took more than 10,000 IU (international units) of Vitamin A daily (twice the FDA recommended daily value) in the first two months of pregnancy had more than double the risk of having a baby with birth defects similar to those seen in Accutane exposed babies (such as a cleft lip or palate, hydrocephalus, or heart defects).<sup>134</sup> Another study conducted at the Boston University School of Medicine compared vitamin A intake during pregnancy in women who had given birth to healthy infants or who had cranial-neural-crest defects (head or face defects), neural tube defects (defects in brain or spinal cord), or

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United States. And, unlike other prescription drugs that carry risks of birth defects, such as epilepsy or anticancer medications, Accutane is not a treatment for a life-threatening condition. No woman on Accutane who gets pregnant can comfort herself with the knowledge that her baby's exposure was incidental to lifesaving treatment." Rafshoon, *supra* note 9.

<sup>127</sup>M.A. Honein et al., *supra* note 125.

<sup>128</sup>Rafshoon, *supra* note 9.

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

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

<sup>131</sup>*Id.*

<sup>132</sup>*Accutane and Other Retinoids: Public Health Education Information Sheet*, March of Dimes, available at [http://www.noah-health.org/english/pregnancy/topics/march\\_of\\_dimes/pre\\_preg.plan/accutane.html](http://www.noah-health.org/english/pregnancy/topics/march_of_dimes/pre_preg.plan/accutane.html).

<sup>133</sup>An excellent overview of the teratogenicity associated with vitamin A can be found at "Recommendations for Vitamin A Use During Pregnancy," 35 *TERATOLOGY* 269-275 (1987).

<sup>134</sup>*Supra* note 132.

defects of the bones, muscles, or urinary tract.<sup>135</sup> The study found that women who took about 10,000 IU or more of vitamin A during pregnancy were more likely to give birth to a child with a cranial-neural-crest defect.<sup>136</sup> The conclusion of this study was that high dietary intake of preformed vitamin A appears to be teratogenic. Among the babies born to women who took more than 10,000 IU of preformed vitamin A per day in the form of supplements, had about a 1 in 57 chance of a malformation attributable to the ingestion of the vitamin A supplement.<sup>137</sup> Longer term effects of Accutane use of pregnant mothers on their children are still uncertain. However, a comprehensive study is being conducted by Dr. Jane Adams of the University of Massachusetts-Boston and Dr. Edward J. Lammer of Stanford University, following 50 children nationwide who were exposed to the drug while in the womb.<sup>138</sup> They hypothesize that although physical abnormalities bypass some of these children, many suffer from learning disabilities including problems with visual perception, spatial processing, and other behavioral issues.<sup>139</sup> They hope to establish a link between the development of learning disabilities and the use of teratogenic drugs such as Accutane.<sup>140</sup>

As stated earlier, upon the introduction of Accutane to the market, the FDA and Roche, the manufacturer of Accutane, began to receive a number of adverse reports about severe birth defects. This was no surprise however since when the FDA first considered Roche's application to sell Accutane two decades ago, agency officials were fully aware that it could potentially cause birth defects.<sup>141</sup> Roche had provided the FDA with

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<sup>135</sup> *Vitamin A*, Center for the Evaluation of Risks to Human Reproduction (CERHR), 5/20/02 available at [http://cerhr.niehs.nih.gov/genpub/topics/vitamin\\_a-ccae.html](http://cerhr.niehs.nih.gov/genpub/topics/vitamin_a-ccae.html). "Between October 1984 and June 1987, the coordinators of the study identified 22,748 pregnant women when they underwent screening either by measurement of maternal serum alpha-fetoprotein or by amniocentesis. Nurse interviewers obtained information on the women's diet, medications, and illnesses during the first trimester of pregnancy. . . Information on the outcomes of the pregnancies were derived from the obstetricians who delivered the babies or from the women themselves. Of the 22,748 women, 339 had birth defects, and 121 had defects occurring in sites that originated in the cranial neural crest." Kenneth J. Rothman, Lynn L. Moore, Martha R. Singer, Uyen-Sa D.T. Nguyen, Salvatore Mannino, & Aubrey Milunsky *Teratogenicity of Vitamin A Intake*, 333 NEW ENG. J. MED 1369-1373 (November 23, 1995).

<sup>136</sup> Center for the Evaluation of Risks to Human Reproduction, *supra* note 135.

<sup>137</sup> Rothman, et al., *supra* note 135.

<sup>138</sup> "Professor Studies Birth Defects of Accutane," Jane Adams available at <http://www.umb.edu/news/1997news/reporter/ureporter1197/accutan>

<sup>139</sup> *Id.*

<sup>140</sup> *See id.*

<sup>141</sup> Rafshoon, *supra* note 9.

test results showing that laboratory animals that were fed isotretinoin, gave birth to deformed offspring.<sup>142</sup> The FDA felt that the effectiveness of the drug outweighed the risks of use, acknowledging that all drugs had side effects and that responsibility for proper use should be shared among the FDA, the manufacturer, prescribing physicians, and the consumer.<sup>143</sup> As the consequences of improper use became startlingly real and reports of birth defects multiplied<sup>144</sup>, the FDA made the decision not to remove the product from the market (as in the thalidomide situation in Europe) but to increase the amount of education, improve labeling, and establish more stringent precautionary measures.

### **Regulation and Other Precautions to Prevent Accutane-Related Birth Defects**

The risk of birth defects in women who become pregnant while using Accutane (isotretinoin) has led to a number of precautionary measures put in place by the Food and Drug Administration. There are a number of guidelines that the FDA put in place that actually dropped the rates of pregnancy in women taking the drug despite an increased use by women of childbearing age.<sup>145</sup> But considering the continued risks of Accutane along with ever-increasing use of this treatment, the FDA and even Roche itself, have instituted a number of other efforts at risk management.

There has long been a Food and Drug Administration effort to monitor and study adverse reactions to drugs.

In fact, reports from doctors (and secondarily, patients) are the FDA's primary means of learning about

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<sup>142</sup>*Id.*

<sup>143</sup>Woodcock, *supra* note 16.

<sup>144</sup>A 1990 FDA memo concluded that as a result of Accutane's risks of birth defects, "The magnitude of injury and death has been great and permanent, with 11,000 to 13,000 Accutane related abortions and 900 to 1,100 Accutane-related birth defects." *Supra* note 55.

<sup>145</sup>*Issues Relating to the Safety of Accutane: Hearing Before the Subcomm. On Oversight and Investigations of the House Committee on Energy and Commerce, 108<sup>th</sup> Cong. (December 11, 2002)*(testimony of Diane S. Berson M.D., Assistant Professor of Dermatology at Joan and Sanford I. Weill Medical College, Cornell University).

adverse reactions to drugs that have already been approved for marketing.<sup>146</sup> This process and the resulting data collection is called the Adverse Event Reporting System (AERS).<sup>147</sup> AERS is a computerized database of post-marketing adverse events for all approved drug and therapeutic biologic products.<sup>148</sup> Currently, AERS contains almost 23,000 reports for Accutane from approval in 1982 to December of 2002.<sup>149</sup> Among the five most commonly reported adverse reactions in these reports during this time period are, in descending order, alopecia, depression, headache, dry skin, and induced abortion.<sup>150</sup> In 2002 alone, the five most frequently reported reactions are again, in descending order, depression, pregnancy, induced abortion, suicidal ideation, and headache.<sup>151</sup> The Office of Drug Safety of the FDA carefully monitors AERS, keeping a cumulative count of Accutane-exposed pregnancies and resulting defects and psychiatric adverse event reports.<sup>152</sup> However, there are numerous problems with this system for reporting adverse reactions to drugs. One problem is that many physicians are not even aware that such a reporting system exists and therefore do not report adverse reactions to medication that occur to their patients.<sup>153</sup> Another problem is that the system as currently configured, is unnecessarily inefficient. Dr. Murray Lumpkin, the former deputy director of the FDA's Center for Drug Evaluation and Research, stated that the agency receives almost 200,000 reports of possible adverse drug reactions, of which a little more than 10 percent of them involving serious reactions that were not seen in clinical trials.<sup>154</sup> Unfortunately, despite this volume, the system is not fully computerized<sup>155</sup> and reports come in as "200,000 pieces of paper."<sup>156</sup> Although the reporting system is by no means perfect, the data that has been collected is helpful to FDA researchers, who can respond to reports that require further

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<sup>146</sup>Gina Kolata, *The F.D.A. Approves a Drug. Then What?*, N.Y. TIMES, October 7, 1997, at F-1.

<sup>147</sup>Woodcock, *supra* note 16.

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

<sup>149</sup>*Id.*

<sup>150</sup>*Id.*

<sup>151</sup>*Id.*

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

<sup>153</sup>Kolata, *supra* note 146.

<sup>154</sup>*Id.*

<sup>155</sup>The system consists of a computerized database but data collection is through written reports that are collected manually and entered into the system.

<sup>156</sup>Kolata, *supra* note 146.

investigation, monitor databases of patients, and then send an alert to physicians if necessary. But data collection is only the beginning.<sup>157</sup> Increased monitoring and surveillance of Accutane users is necessary to prevent potentially tragic side effects.

In 1989, Roche implemented the Pregnancy Prevention Program (PPP) to prevent fetal exposure to Accutane.<sup>158</sup> This program instructed prescribing physicians that “women of childbearing potential should:

1.

Have two negative pregnancy tests

2. Use two forms of birth control simultaneously, starting one month before the prescription. Consequently, Accutane treatment should then begin only after the second or third day of the next cycle.

3. Be capable of comprehending and carrying out these instructions.

4. Receive both verbal and written warnings of the risks of exposing the fetus to Accutane.”<sup>159</sup>

One problem with the PPP is that its use by physicians was entirely voluntary.<sup>160</sup> A Survey of Accutane Use in Women commissioned by Roche discovered that compliance with the PPP was poor and as a result there was little reduction in the number of pregnancies during Accutane use.<sup>161</sup> Between the period of

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<sup>157</sup> *Id.*

<sup>158</sup> Martinez, *supra* note 7.

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

<sup>160</sup> *Id.*

<sup>161</sup> *Id.* “Women treated with Accutane were encouraged to enroll in the survey through their physician by filling out a form in the medication package or by calling a toll-free telephone number. . . They were randomly assigned to be followed by telephone or by mail. . . As of August 2000, the survey reported results on 494,915 women. The pregnancy rate among these women was 2.8 per 1000 140-courses of isotretinoin. Among 28,016 women evaluated between 1995 and 2000, 195 identified themselves

1982 and 2000, Roche received reports of 1,995 Accutane exposed pregnancies.<sup>162</sup> Since the PPP went into effect in 1989 through 2000, the FDA's Adverse Events Reporting System database has reported 20 cases of congenital abnormalities and 89 abortions (both spontaneous and induced) per year on average due to prenatal exposure to Accutane.<sup>163</sup> In comparison, another pregnancy program initiated to deal with another teratogenic medication, Thalidomide, has been tremendously more successful.<sup>164</sup> This program, unlike the PPP, requires *mandatory* registration of prescribing physicians, patients, and pharmacies in addition to *mandatory* compliance with the program.<sup>165</sup> As of 2002, no pregnancies have been reported among 360 sexually active women who are of reproductive age and currently taking Thalidomide.<sup>166</sup> The possibility of transferring the successful pregnancy program for Thalidomide to Accutane is unlikely due to issues of scale. Thalidomide, having never been marketed in the United States due to the European tragedy, is not widely accessible.<sup>167</sup> It was only recently, in July of 1998, that the FDA approved the use of Thalidomide only for the treatment of debilitating and disfiguring lesions associated with Hansen's disease, otherwise known as leprosy.<sup>168</sup> The prescription of thalidomide is limited only to those individuals. Accutane, on the other hand, has been prescribed for 5 million Americans since its approval, with these numbers increasing rapidly.<sup>169</sup> It may be impracticable to expect that certain mandatory safety measures, successful with a limited number

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as being sexually active and not practicing contraception. Nearly all women in the Survey were advised to avoid pregnancy while taking Accutane and 75% of the sexually active women had signed a consent form. Nevertheless, only 67% of the women postponed starting treatment until the results of a pregnancy test were known and only 57% of the women surveyed postponed treatment until their next menstrual period as instructed by the PPP." *Id.*

<sup>162</sup>Martinez, *supra* note 7.

<sup>163</sup>*Id.*

<sup>164</sup>*Id.*

<sup>165</sup>*Id.*

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

<sup>167</sup>Herbert Burkholz, *Giving Thalidomide a Second Chance*, FDA CONSUMER MAG., (September-October 1997), available at [http://www.fda.gov/fdac/features/1997/697\\_thal.html](http://www.fda.gov/fdac/features/1997/697_thal.html). "That thalidomide was never marketed in the United States was largely due to the stubborn skepticism of FDA's Frances Kelsey, M.D., Ph.D., whose doubts about the drug kept it out of American pharmacies. Assigned to review the thalidomide application, she fought a dogged defensive battle, blocking and parrying every attempt by Richardson-Merrell to gain approval until the news from the European countries made approval unthinkable."

<sup>168</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* (December 16, 2002), available at <http://www.fda.gov/cder/news/thalinfo/default.htm>.

<sup>169</sup>Mary Duenwald, *Debate on Acne Drug's Safety Persists Over Two Decades*, N.Y. TIMES, January 22, 2002, at F-7.

of Thalidomide users, could be applicable to the millions of users of Accutane.

Another such effort is the institution of the S.M.A.R.T. program.<sup>170</sup> This program was intended at meeting two principal goals articulated by an FDA advisory committee on the use of Accutane in September 2000: that no woman should begin Accutane therapy if she is pregnant and no pregnancies should occur while a woman is actually taking Accutane.<sup>171</sup> The FDA sought to involve individuals at all levels, from consumers and patients to physicians and pharmacists.

The S.M.A.R.T. program stands for the System to Manage Accutane Related Teratogenicity.<sup>172</sup> Under the S.M.A.R.T. program, pharmacists dispense Accutane only upon the presentation of a prescription with the special yellow isotretinoin qualification sticker.<sup>173</sup> This special yellow sticker is affixed to the prescription the prescriber, who is essentially asserting that the conditions in the labeling have been met and the patient is therefore “qualified” to receive the drug.<sup>174</sup> This means that a female patient has a negative pregnancy test each month, has received repeat counseling about pregnancy avoidance and birth defects, has chosen and agreed to use two effective forms of contraception or abstinence, and has been encouraged to join a follow-up survey to monitor program performance.<sup>175</sup> For a physician to obtain the yellow stickers in the first place, they must agree to cooperate with this program and attest to their ability to manage a teratogenic drug.<sup>176</sup> S.M.A.R.T. includes a number of other tools to help patients, physicians, and pharmacists manage the risk of birth defects in Accutane use. These include an updated second medical consent form for female patients, a Medication guide, a patient video, separate patient education kits for both men and women, and guides for both physicians and pharmacists.<sup>177</sup> Additionally, an important component of this effort is a survey on female patients’ experience with Accutane. Female patients are encouraged by the physicians to complete

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<sup>170</sup>Woodcock, *supra* note 16.

<sup>171</sup>*Id.*

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

<sup>173</sup>*Id.*

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

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

<sup>176</sup>*Id.*

<sup>177</sup>*Id.*

survey forms that are analyzed by the FDA to measure the success and effectiveness of efforts to manage the risk of pregnancy in female isotretinoin patients.<sup>178</sup>

This program is based on a “three-fold partnership” according to the FDA, at the physician, pharmacist, and patient levels.<sup>179</sup> This partnership and the requirements that go along with it should enhance the overall likelihood of attaining the goals articulated by the FDA advisory committee on the use of Accutane. As of now, any preventative effect of this program is not yet clear although several independent assessments are being conducted to measure effectiveness. One such assessment is the aforementioned isotretinoin patient survey. Another assessment is an independent audit of pharmacies to assess the use of Accutane Qualification Stickers by physicians.<sup>180</sup>

Although the S.M.A.R.T. program has been a great improvement in insuring that the use of Accutane is sufficiently regulated to prevent birth defects, there is still criticism that the program can do more. According to the Congressional testimony of Lynn Martinez, the Manager of the Teratology and Birth Defects Program at the Utah Department of Health, although physicians are required to register with Roche, no consequences are specified for those fail to register.<sup>181</sup> Additionally, although patients are encouraged to enroll in the Accutane survey, it is not mandatory.<sup>182</sup> There are also no safeguards in place to ensure that pharmacists only fill prescriptions that have a yellow sticker.<sup>183</sup> Many of the “requirements” of the S.M.A.R.T. program lack the consequences that will ensure optimal compliance – so in a sense, these requirements are not requirements at all. So despite this program and the accompanying regulations, pregnancies while using Accutane treatments still can – and do – occur. Unfortunately, imposing sanctions or fines for physician or patient non-compliance would be significant government intrusion into a physician-patient relationship and

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<sup>178</sup>Berson, *supra* note 145.

<sup>179</sup>Woodcock, *supra* note 16.

<sup>180</sup>*Id.*

<sup>181</sup>Martinez, *supra* note 7.

<sup>182</sup>*Id.*

<sup>183</sup>*Id.*

may be difficult, if not impossible to enforce.<sup>184</sup>

## V. ACCUTANE AND DEPRESSION/SUICIDAL IDEATION

### *Is there a Link Between Accutane Use and Depression? – Recent Developments*

On January 5, 2002, four months after the September 11<sup>th</sup> attacks, Charles Bishop, a fifteen-year old, crashed a Cessna plane into the 28<sup>th</sup> floor of the Bank of America building in Tampa, Florida.<sup>185</sup> Bishop had flown without permission from a flight school at the St. Petersburg-Clearwater International Airport, where he left a suicide note behind.<sup>186</sup> At the time of this suicide, Bishop had a prescription for Accutane and his family contends that the use of this drug made him psychotic and suicidal.<sup>187</sup> Peter McNulty, an attorney for the Bishop family stated that as a result of taking the drug, Mr. Bishop “became severely psychotic and lost touch with reality, consequently, flying into the side of a building.”<sup>188</sup>

Julie Bishop, the mother of Charles Bishop, recently filed a lawsuit against the manufacturer of Accutane,

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<sup>184</sup>In her testimony, Martinez is critical of the current S.M.A.R.T. guidelines and simply suggest making mandatory physician enrollment in the S.M.A.R.T. program and patient and physician participation in an independent registry established to monitor compliance. However, this begs the question, “How?” Martinez offers no suggestions on possible sanctions or disciplinary measures for noncompliance. She suggests utilizing the Thalidomide S.T.E.P.S. program as a template, but fails to acknowledge that Thalidomide regulation takes place on an exponentially smaller scale than a similar program would for Accutane. *See id.* See also Center for Drug Evaluation and Research, *supra* note 168.

<sup>185</sup>Dana Canedy, *Mother of Teenage Suicide Pilot Sues Maker of Acne Drug She Says He Used*, N.Y. TIMES, April 17, 2002, at A-14.

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

<sup>187</sup>*Id.*

<sup>188</sup>*Id.*

Hoffman-La Roche Inc., seeking \$70 million in damages and arguing that the drug maker was aware that Accutane can cause severe depression, psychosis, and suicidal tendencies but has kept it on the market anyway, without adequately warning users.<sup>189</sup> The lawsuit further contends that since the introduction of Accutane to the U.S. market, more than 500 adverse reactions have been recorded by national and international health agencies – and Hoffman-La Roche has not done enough to inform consumers and prevent the occurrence of these adverse reactions.<sup>190</sup>

Other families have blamed Accutane for causing suicide. Most notably, the son of Congressman Bart Stupak, a Democrat from Michigan, committed suicide in May 1999 at the age of 17.<sup>191</sup> At the time, BJ Stupak had been using Accutane. In a press conference, Congressman Stupak made a statement about what he believed to be a link between his son’s death and the use of Accutane.<sup>192</sup> He emphasized that BJ had never exhibited signs of depression and was generally, “successful, popular, and full of enthusiasm for life.”<sup>193</sup> But when BJ committed suicide, Congressman Stupak and his wife suspected a link to his use of Accutane. In their own independent research, the Stupak family discovered that a number of adverse events had caused the FDA to strengthen the warning on the Accutane label to include the risk of psychosis and suicidal thoughts and actions.<sup>194</sup> Stupak found that his son’s Accutane package contained no warning as to the risk of depression or suicide.<sup>195</sup> Congressman Stupak has since become a visible and vocal advocate for increased FDA regulation of Accutane and improving the amount of information available to potential consumers. Stupak has utilized his position in Congress to publicize the story of his son and others who have experienced similar tragedies related to Accutane use.<sup>196</sup> His initiative has led to a number of Congressional

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<sup>189</sup> *Id.*

<sup>190</sup> *Id.*

<sup>191</sup> Duenwald, *supra* note 169.

<sup>192</sup> Statement of Rep. Bart Stupak, Press Conference, October 5, 2000, available at [http://www.house.gov/stupak/accutane\\_stupak\\_statement.htm](http://www.house.gov/stupak/accutane_stupak_statement.htm).

<sup>193</sup> *Id.*

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

<sup>195</sup> *Id.*

<sup>196</sup> Duenwald, *supra* note 169.

hearings on the safety and regulation of Accutane.

These two tragedies, receiving substantial coverage by the media, along with a number of studies and adverse event reports, lead to the question: What exactly is the causal connection between Accutane use and depression/suicide? Even FDA officials acknowledge that there is no official proof that Accutane causes depression.<sup>197</sup> However, the FDA did count a number of patients who became depressed while taking Accutane, and then found that their depression disappeared after they stopped taking the medication and recurred when they resumed taking it.<sup>198</sup>

A number of studies and reporting systems seem to indicate that evidence of a potential causal link between Accutane and depression/suicide is not merely anecdotal. A recent MEDLINE search of isotretinoin therapy and its effects on mood from 1980-1998 revealed 24 cases of psychological distress associated with the use of the drug.<sup>199</sup> An earlier study from 1983 has shown that 5.5% of patients using isotretinoin suffered depressive symptoms including the occurrence of malaise, crying spells, and forgetfulness within two weeks of beginning isotretinoin treatments.<sup>200</sup> These studies have not been limited to the United States. Adverse drug reaction information has been collected worldwide through the World Health Organization, UK Medicines Control Agency, and the manufacturer of Accutane itself, Roche.<sup>201</sup> The potentially depressive side effects of Accutane were compared against the effects of five other common prescription acne medications.<sup>202</sup> Worldwide, there were 1,830 reports of psychiatric events attributable to these six medications, of which Accutane was implicated in 59.8%.<sup>203</sup> Forty-seven cases of suicide and fifty-six cases of suicidal ideation were reported

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<sup>197</sup> *Id.*

<sup>198</sup> Associated Press, *An Acne Drug and Depression May be Linked*, N.Y. TIMES, February 26, 1998, at A-15.

<sup>199</sup> Tzarina Middelkoop, *Roaccutane (Isotretinoin) and the Risk of Suicide: Case Report and a Review of the Literature and Pharmacovigilance Reports*, 12 J. OF PHARMACY PRAC. 1 (October 1999).

<sup>200</sup> *Id.*

<sup>201</sup> *Id.*

<sup>202</sup> These other medications reviewed along with Accutane were Dianette, Doxycycline, Minocycline, Oxytetracycline, and Tetracycline. *Id.*

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

in association with Accutane use, with no other incidents of suicide or suicidal ideation being reported for any of these other medications.<sup>204</sup> A very recent examination of serious adverse events from Accutane use in the United States indicates that there continue to be cases of suicide and suicidal ideation arising from Accutane use. From 1998 to 2000, there were 54 reported cases of suicides, and 111 reported incidents of suicide ideation associated with Accutane use.<sup>205</sup> During that time, the number of suicides declined but the number of incidents of suicidal ideation during that time remained constant during that three-year period.<sup>206</sup> Additionally, there were 160 cases of hospitalization reported due to Accutane use during that time period.<sup>207</sup> Anecdotal evidence coupled with these existing statistics and studies was enough of a link to prompt a new precautionary warning for Accutane according to the FDA, despite the fact that a conclusive link between Accutane and depression had not yet been proven.<sup>208</sup>

Although a conclusive link has not been proven, a circumstantial scientific link can be shown. The active ingredient in Accutane, isotretinoin, is a member of the family of compounds called retinoids.<sup>209</sup> Isotretinoin is an analog of Vitamin A (retinol) and shares many of the side effects associated with Vitamin A.<sup>210</sup> Some of the side effects of an excess of Vitamin A include irritability, headache, fatigue, vomiting, and dry skin.<sup>211</sup>

Interestingly, certain psychiatric side effects have been associated with Vitamin A intoxication. There have

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<sup>204</sup> *Id.*

<sup>205</sup> *Accutane Serious Adverse Events 1998-2000*, Adverse Event Reporting System, Food and Drug Administration, August 3, 2000, available at [http://www.house.gov/stupak/images/accutane\\_summary\\_adverse\\_events.pdf](http://www.house.gov/stupak/images/accutane_summary_adverse_events.pdf).

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

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

<sup>208</sup> Roche was instructed by the FDA to send a letter to thousands of doctors informing them of the new Accutane label which states that “Accutane may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts, and suicide.” Associated Press, *supra* note 198.

<sup>209</sup> Middelkoop, *supra* note 199.

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

<sup>211</sup> *Id.* “An intake of retinoids greatly in excess of that required by the body results in a toxic syndrome known as hypervitaminosis A. There are two types of Hypervitaminosis A, acute and chronic. Acute hypervitaminosis A results from ingestion of a very high dose of vitamin A over a short period of time. Typical symptoms include bulging fontanels in infants and headache in adults, nausea, vomiting, fever, vertigo, and visual disorientation. Chronic hypervitaminosis A is more common than the acute form and results from continued ingestion of high doses for months or even years. Symptoms include anorexia, dry itchy skin, alopecia, increased intracranial pressure, fatigue, irritability, somnolence pronounced craniofacial and occipital edema, skin desquamation, fissuring of the lips, pain in the legs and forearms, neurologic disturbances and lethargy. Elevated blood levels are also common. This reads just like the Accutane package insert.” *Accutane – Is This Acne Drug Treatment Linked to Depression and Suicide: Hearing Before the House Comm. on Committee on Government Reform*, 106<sup>th</sup> Cong 259, 264 (December 5, 2000) (testimony of Dr. James O’Donnell, Assistant Professor of Pharmacology at Rush Medical College).

been a number of case studies and reports indicating that excess Vitamin A intake could lead to the onset of prolonged depression, mood swings, insomnia, fatigue, and irritability.<sup>212</sup> These findings may indicate that the link between Accutane (isotretinoin) and depression at the very least, merits further study, and may ultimately indicate the existence of psychiatric side effects from Accutane use.

Representatives of the manufacturers of Accutane, Roche (or Hoffman-La Roche, Inc.) assert that any potential link between Accutane use and depression/suicide are overblown. Although acknowledging that further study and certain precautionary steps are necessary, the President and Chief Executive Officer of Hoffman-La Roche, Inc., George B. Abercrombie, has asserted that the psychiatric adverse events associated with Accutane may simply be the result of the fact that the Accutane patient population is already susceptible to psychiatric problems whether or not Accutane is actually used.<sup>213</sup> In Congressional testimony, he emphasized that according to the Surgeon General's 2001 National Strategy for Suicide Prevention, suicide among young people aged 15-24, who make up a large part of the population prescribed Accutane, is already an enormous public health problem.<sup>214</sup> He asserted that it is generally difficult, if not impossible, to discern whether suicidal events can be directly related to medication consider the complex range of behavioral, genetic, and environmental factors involved in depression and suicidal ideation.<sup>215</sup> Abercrombie stated that considering this difficulty it was important to emphasize that "Indeed, even using conservative assumptions, the rate of psychiatric events [depression and suicide] in the Accutane patient population does not appear

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<sup>212</sup> *Id.* at 265. A case report was published regarding a 54-year old female with no past psychiatric history and no family history of affective disorder. After a regular vitamin supplementation of Vitamin A (25,000 IU), she began exhibiting signs of a depressed mood, poor concentration, frequent tearfulness, and guilty rumination. . . The patient was instructed to discontinue vitamin A and was seen 2 and 4 weeks later. . . Progressive improvement in the physical symptoms and full remission of depressive symptoms occurred at 2 months. Ellnore F. McCance Katz & Lawrence H. Price, *Depression Associated With Vitamin A Intoxication*, 33 PSYCHOSOMATICS 117 (Winter 1992).

<sup>213</sup> Abercrombie, *supra* note 25.

<sup>214</sup> *Id.* Abercrombie emphasized that, "For young people 15-24 years old, suicide is the third leading cause of death, behind unintentional injury and homicide. Every 17 minutes, another life is lost to suicide. Every day, 86 Americans take their own life and over 1500 attempt suicide. There are no twice as many deaths due to suicide than due to HIV/AIDS. For every completed suicide, there are five hospitalizations and 22 Emergency Department visits for suicidal behaviors –over 670,000 visits in a year."

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

to deviate from the background incidence of such events in a comparative population.”<sup>216</sup>

Hoffman-La Roche took affirmative step toward proving the accuracy of these statements by sponsoring a study investigating the proposed association between Accutane use and the risk of depression and suicide. This study is referred to as the *Jick Study* and was published in 2000 and conducted by Dr. Susan S. Jick, Dr. Hilal Maradit Kremers, and Ms. Catherine Vasilakis-Scaramozza.<sup>217</sup> In this study, data were analyzed from 7,535 isotretinoin users and 14,376 oral antibiotic users with acne from Canada and the United Kingdom.<sup>218</sup> Prevalence rates of neurotic and psychotic disorders, suicide, and attempted suicide were compared between isotretinoin and antibiotic users and within isotretinoin users as their own comparison, between pre-treatment and post-treatment.<sup>219</sup> The study concluded that there was no evidence that use of isotretinoin is associated with an increased risk for depression, other psychiatric disorders, or suicidal behavior.<sup>220</sup> According to the study, the relative risk estimates for newly diagnosed depression or psychosis were the same whether a patient used isotretinoin or not.<sup>221</sup>

Critics of this study point out that this study was funded wholly by Hoffman-La Roche, the manufacturer of Accutane, which has a strong financial interest in establishing any evidence that isotretinoin does not have any link to depression or suicide. However, the concerns about this study are less about bias and more about methodology. Dr. Diane Wysowski of the FDA also criticized the methodology of the *Jick Study*, emphasizing that the sample size was too small to “generate stable estimates for suicide and attempted suicide.”<sup>222</sup> Wysowski stated that other problems included under-ascertainment of psychiatric disorders and suicides, lack of data on dose and duration of isotretinoin treatments, and the lack of a control group without

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

<sup>217</sup> Susan J. Jick, Hilal Maradit Kremers, & Catherine Vasilakis-Scaramozza, *Isotretinoin Use and the Risk of Depression, Psychotic Symptoms, Suicide and Attempted Suicide*, 136 ARCHIVES OF DERMATOLOGY 1231-1236 (October 2000). Available at <http://www.accutaneaction.com/jickstudy.pdf>.

<sup>218</sup> *Id.* at 1231.

<sup>219</sup> *Id.*

<sup>220</sup> *Id.* at 1234.

<sup>221</sup> *Id.* at 1231, 1234.

<sup>222</sup> Diane K Wysowski, *Methodological Limitations of the Study ‘Isotretinoin Use and Risk of Depression, Psychotic Symptoms, Suicide, and Attempted Suicide,’* 137 ARCHIVES OF DERMATOLOGY 1102 (August 2001).

acne.<sup>223</sup> She also pointed out that the results have limited applicability to the United States because the recommended doses for Accutane in the United States are significantly higher than in Canada and England.<sup>224</sup> Wysowski asserted that these limitations of the *Jick Study* render the findings inconclusive and further study is necessary.<sup>225</sup> However, a conclusive result could take years while adverse psychiatric reactions continue to be reported and Accutane use increases – indicating a need for further precautionary measures independent of any statistical findings.

## The FDA and Manufacturer’s Response to Concerns about Depression

Several precautions have been taken by both the FDA and the manufacturer of Accutane, Roche, to inform potential consumers of the psychiatric risks sometimes associated with Accutane use. As concerns increased about the proven harm that could result from Accutane use by pregnant women, the labeling of Accutane was modified to provide information on these risks to potential consumers. In the same way, as reports of psychiatric dangers of Accutane circulated, the labeling of Accutane was changed to provide information on these potential risks, despite the lack of any definitive causal link. Changing labeling may not affirmatively prevent suicide, but it may allow patients to choose an alternative means of acne treatment if they are already prone to depression or suicidal ideation. If properly warned through labeling, patients may also be

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<sup>223</sup> *Id.* “Because there was no control group without acne, a result of no difference in rates of depression between the groups might be due to an effect of acne.” *Id.*

<sup>224</sup> *Id.* “The maximum recommended does in the United States is 2mg/kg per day compared with 1 mg/kg per day in England and 2mg/kg per day in exceptional instances in Canada. In England, isotretinoin is restricted to hospitals only and is prescribed by dermatologists or under the supervision of consultant dermatologists. Consequently, patients prescribed isotretinoin would not be fully represented in the general practice research database.” *Id.*

<sup>225</sup> *Id.*

able to recognize changes in their mood or emotional condition and either modify or discontinue Accutane treatment if they feel that it may be causing such changes. Providing as much information in the labeling as possible about potential side effects enables patients to make informed choices about the manner and continuance of treatment – especially if depressive symptoms arise.

Beginning in 1983, Roche began receiving occasional reports of psychiatric adverse events in patients who were taking Accutane or who had taken Accutane recently.<sup>226</sup> Roche then began submitting these reports to the FDA and according to Roche, in December 1984, they approached the FDA to request that the professional labeling information for Accutane be revised to include the reports of depression and emotional instability in the Accutane patient population.<sup>227</sup> Roche reports that in both 1985 and 1986, it sent letters to the medical community describing the changes to the labeling of Accutane relating to incidents of severe depression.<sup>228</sup> During this time, the patient brochure and other components of Accutane packaging specifically alerted patients to be aware of potential changes in mood during Accutane treatment and to alert their physician if such changes did occur anytime throughout the course of treatment.<sup>229</sup> Again in 1998, Roche and FDA met together to review adverse events reporting and consider changes to Accutane labeling.<sup>230</sup> As a result of this meeting, the label of Accutane was changed to include this warning:

*“Psychiatric disorders: Accutane may cause depression, psychosis, and rarely, suicidal ideation, suicide attempts, and suicide. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary. No mechanism of action has been established for these events.”*<sup>231</sup>

Additionally, the Adverse Reaction language on the potential nervous system effects was amended to include the risk of depression and suicide.<sup>232</sup> Roche also distributed a Dear Doctor letter to prescribers in order to point out the new language on suicide and depression in the package insert.<sup>233</sup>

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<sup>226</sup> Abercrombie, *supra* note 25.

<sup>227</sup> *Id.*

<sup>228</sup> *Id.*

<sup>229</sup> *Id.*

<sup>230</sup> *Id.*

<sup>232</sup> *Id.*

<sup>233</sup> *Id.*

The FDA, along with Roche, has undertaken a patient education effort to lessen the potential risk of Accutane use. In January of 2001, the FDA developed a “Medication Guide” for Accutane in consultation with Roche.<sup>234</sup> Pharmacists must distribute this guide to every Accutane patient each time an Accutane prescription is dispensed.<sup>235</sup> It summarizes in layperson’s language, the information normally available in the Professional Package Insert including the approved indication for Accutane and major adverse events reported in the package insert.<sup>236</sup> Essentially, this guide serves as a reminder of the proper use of the drug, specifying some warning signs for the course of the treatment and explicitly stating the risks.<sup>237</sup> Currently, an “informed consent” form is now provided to all patients who have been prescribed Accutane.<sup>238</sup> This form is intended to be used by the prescribing physician after that physician has determined that a patient may be a candidate for Accutane and has adequately explained the proper use of the medication and its possible side effects. The informed consent form clearly states that some patients have reported that they became depressed or developed serious mental problems, including suicidal ideation, while taking Accutane and some individuals have ended their lives.<sup>239</sup> Patients read the information presented, which is also explained by the prescribing physician, and initial each of the items on the form and sign and date the entire form, acknowledging that they understand all of the information presented.<sup>240</sup> The prescribing

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<sup>234</sup> *Id.*

<sup>235</sup> Woodcock, *supra* note 16.

<sup>236</sup> *Id.*

<sup>237</sup> Abercrombie, *supra* note 25. This medication guide explicitly states in a section entitled “Mental Problems and suicide,” that “Some patients, while taking Accutane, have become depressed or developed other serious mental problems. Signs of these problems include feelings of sadness, irritability, unusual tiredness, trouble concentrating, and loss of appetite. Some patients taking Accutane have had thoughts about hurting themselves or putting an end t their own lives (suicidal thoughts). Some people tried to end their own lives. And some people ended their own lives. There were reports that some of these people did not appear depressed. No one knows if Accutane caused these behaviors or if they would have happened even if the person did not take Accutane.” *Id.*

<sup>238</sup> This informed consent form serves the dual purpose of informing the consumer and physician and also protecting Roche from liability. Failure to instruct or warn is the major basis of liability for manufacturers of prescription drugs and medical devices. The Restatement (Third) of Torts: Products Liability states a traditional rule that in most cases, drug manufacturers are liable only when their products are sold without adequate instructions and warnings to health care providers; patients do not need to be warned directly by the manufacturer (“learned intermediary doctrine”). The informed consent form thus protects both the physician and the manufacturer from liability by insuring that the patient has been informed of all the risks. See Andrew E. Falsetti, *Fluoxetine-Induced Suicidal Ideation: An Examination of the Medical Literature, Case Law and the Legal Liability of Drug Manufacturers*, 57 FOOD & DRUG L.J. 273, 290 (2002).

<sup>239</sup> *Id.*

<sup>240</sup> Woodcock, *supra* note 16.

physician also signs and dates this form.<sup>241</sup> In the case of minors, a parent or guardian must also sign the form and consent to treatment.<sup>242</sup> The signed and dated forms are then placed in the patient's medical records.<sup>243</sup> These informed consent forms and the accompanying Medication guide have gone to over 350,000 physicians, 130,000 pharmacists and 55,000 pharmacies.<sup>244</sup>

Both the FDA and Roche have made other attempts at patient education. The FDA has established an Accutane information web page on the FDA website geared toward potential consumers of Accutane.<sup>245</sup> The FDA also continues to submit scientific papers for publication on the risks associated with Accutane, notifies physicians of updates in regard to labeling or other relevant information, and develops literature in easy-to-understand language for potential consumers.<sup>246</sup> Roche has also funded a major National Mental Health Awareness Campaign focusing on psychiatric concerns, and suicide specifically, in the teenage population.<sup>247</sup> Critics of Roche may argue that these attempts at education pale in comparison with the amount of investment in advertising products like Accutane to the teenage population.<sup>248</sup> So in a sense, Roche may be attempting to combat a problem of its own creation.

Further examination of the side effects of Accutane is necessary to insure that the proper precautionary steps are taken by both the FDA and Roche. This is especially important in the area of depression and suicide, where there is little direct evidence of causality but a growing public concern. Toward that end, two studies are currently being conducted to definitively determine whether a cause and effect relationship exists between Accutane use and suicide. One study is being conducted by a number of doctors and scientists

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<sup>241</sup> Abercrombie, *supra* note 25.

<sup>242</sup> *Id.*

<sup>243</sup> Woodcock, *supra* note 16.

<sup>244</sup> Abercrombie, *supra* note 25.

<sup>245</sup> <http://www.fda.gov/cder/drug/infopage/accutane>.

<sup>246</sup> Woodcock, *supra* note 16.

<sup>247</sup> Abercrombie, *supra* note 25.

<sup>248</sup> Roche has run ad campaigns aimed at increasing awareness of its anti-acne prescription medications on family and youth oriented programming on national cable television, including the Nickelodeon Channel. In 2000, Roche spent over \$8 million on television advertising. Patricia Winters Lauro, *Teenagers Have Largely Escaped Prescription Medicine Promotional Campaigns, Until Now*, N.Y. TIMES C-14 (March 16, 2000).

involved in litigation against Roche. This study is being led by Dr. Donald H. Marks, an Alabama clinical research expert who is a former associate director of clinical research at Roche.<sup>249</sup> He also runs the Extant Medical Group, which specializes in the diagnosis, evaluation, and treatment of adverse events from different types of medication.<sup>250</sup> This study will be conducted by a team of doctors who will investigate as many as 1,000 cases of suicide in the general population to determine how many cases involved the use of Accutane.<sup>251</sup> Those cases would then be compared to at least two other deaths of people of the same sex and age in the general population.<sup>252</sup> According to a doctor assisting Marks with this study, a high percentage of Accutane users among the studied suicides, as opposed to deaths in the general population among similar individuals, would show cause and effect.<sup>253</sup>

The manufacturer of Accutane is in separate talks with the FDA to conduct another study examining a possible link between Accutane use and suicide.<sup>254</sup> Roche would likely conduct the study, but the FDA might require oversight by a group of impartial, outside scientists. Carolyn Glynn, a spokeswoman of Roche, stated, “We have not been able to prove a causal link [between Accutane and suicide]. But this is a serious enough issue that we are working on a proactive study. We want to understand this as much as anybody.”<sup>255</sup> The FDA also began collaboration with the National Institute of Mental Health (NIMH) to address the need for independent research (outside the FDA and Roche relationship) to address the aforementioned Accutane related mental health concerns.<sup>256</sup> On November 19, 2002, NIMH held a workshop to discuss basic scientific research into the effects of retinoids on the central nervous system.<sup>257</sup> As explained earlier, Accutane (isotretinoin) is a retinoid compound. At this workshop, neuroscientists presented preliminary

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<sup>249</sup>Mark Benjamin and Dan Olmstead, Two Studies Probe Suicide, Accutane Link, WASH. TIMES, May, 3, 2002, *available at* <http://www.washtimes.com/upi-breaking/02052002-051045-8597r.htm>.

<sup>250</sup>*Id.*

<sup>251</sup>*Id.*

<sup>252</sup>*Id.*

<sup>253</sup>*Id.*

<sup>254</sup>*Id.*

<sup>255</sup>*Id.*

<sup>256</sup>Woodcock, *supra* note 16.

<sup>257</sup>*Id.* Retinoids are chemical compounds that act on the vitamin A recognition sites in the body. *Id.*

findings from animal and in-vitro studies and concluded that additional research must be done.<sup>258</sup> Such scientific collaboration can guide the design of future clinical studies aimed at identification of risk factors and precautionary options to allow patients who need Accutane to use it with optimal safety.<sup>259</sup>

## VI. REPRESENTATIVE EXAMPLES OF RECENT ACCUTANE LITIGATION

Significant litigation has occurred as a result of the severe side effects of Accutane. Litigants have brought product liability actions against Roche, the manufacturer of Accutane in a number of states. These claims include actions based upon failure to adequately warn about potential birth defects caused by Accutane, the occurrence of seizures or inflammation as a result of ingesting Accutane, and most recently, the incidence of severe depression and suicide linked to Accutane treatments. Many of these cases have been resolved on procedural grounds by both state and federal courts. However, a number of cases have been fully litigated and are meaningful toward an overall analysis of how medical efficacy, corporate distribution, government regulation, and litigation intersect and ultimately how Accutane can be prescribed and utilized in a safe yet efficient manner.

One such case is *Thomas v. Hoffman La-Roche, Inc.*<sup>260</sup> that was originally heard in the United District Court for the District of Mississippi and then on appeal in the 5<sup>th</sup> Circuit. The plaintiff, Mary Kathryn Thomas,

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<sup>258</sup> *Id.*

<sup>259</sup> *Id.*

<sup>260</sup> 949 F.2d 806 (5<sup>th</sup> Cir. 1992)

a 54-year old female, began Accutane treatment in January of 1984 for severe recalcitrant cystic acne.<sup>261</sup> She had been prescribed Accutane by her physician, Dr. Robert P. Meyers, who had treated the plaintiff for several years and had observed that other antibiotics and treatments had little effect on her acne.<sup>262</sup> A few months into her Accutane treatment, Thomas complained of extreme confusion.<sup>263</sup> Subsequently, she was hospitalized for neurological problems in March of 1994.<sup>264</sup> For a number of months, Thomas was transferred to a number of hospitals for neurological issues including the incidence of seizures.<sup>265</sup> During all these periods of hospitalization, the plaintiff was disoriented, at times comatose, sometimes non-responsive, and generally exhibited severe neurological problems.<sup>266</sup>

At the time that Dr. Meyer prescribed Accutane for Thomas, the Physician's Desk Reference, a compilation of FDA-approved prescription package inserts, contained a relatively general entry on Accutane.<sup>267</sup> This entry stated that Accutane should only be reserved for patients with the most untreatable, severe forms of acne and that Accutane was not to be prescribed to pregnant women.<sup>268</sup> Although the entry listed a number of side effects to Accutane use, seizures and neurological disorders in general were not included on this list.<sup>269</sup> When Dr. Meyer prescribed Accutane for Ms. Thomas, there were only ten reported seizures from over 400,000 Accutane users.<sup>270</sup> In the spring of 1984, Hoffman-La Roche released a "Dear Doctor" letter advising physicians that, although there was no evidence that Accutane caused seizures, they would be listed as a potential side effect in a future edition of the Physician's Desk Reference.<sup>271</sup>

Thomas brought a products liability action against Hoffman-La Roche, Inc., the manufacturer of Accutane,

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<sup>261</sup> *Thomas v. Hoffman-La Roche*, 731 F. Supp. 224, 226 (1989).

<sup>262</sup> *Id.*

<sup>263</sup> Michael Ryland Moser, *Case Brief: Thomas v. Hoffman La-Roche, Inc.*, 1 J. PHARMACY & L. 239 (1992).

<sup>264</sup> *Id.*

<sup>265</sup> *Thomas*, 731 F. Supp. at 224, 226.

<sup>266</sup> *Id.* Thomas also experienced fever, disorientation, and seizures prior to each of these hospitalizations. Moser, *supra* note 263.

<sup>267</sup> *Id.*

<sup>268</sup> *Id.*

<sup>269</sup> *Id.*

<sup>270</sup> *Id.*

<sup>271</sup> *Id.* at 239-240.

alleging that the acne drug caused neurological problems and seizures.<sup>272</sup> The plaintiff alleged that the defendant was negligent for failing to warn and that Accutane itself was unreasonably dangerous because of the inadequacy of the manufacturer's warning.<sup>273</sup> At trial, expert witnesses testified that in their opinion, the ingestion by the plaintiff of Accutane caused the seizures.<sup>274</sup> These witnesses testified for the plaintiff that Accutane should have explicitly warned that it should not be prescribed for patients like Thomas.<sup>275</sup> These witnesses also testified that Hoffman-La Roche's warning regarding seizures should have been issued sooner.<sup>276</sup> On Hoffman-La Roche's behalf, testimony was given that the general population was more susceptible to seizures than the small subset of Accutane users as a class.<sup>277</sup> Crucially, Dr. Meyer himself testified that he was aware of the risk of seizures associated with Accutane use and that he would not have altered his recommended course of treatment even if he had been officially warned of the risk.<sup>278</sup> After considering this testimony and other evidence, a jury found Hoffman-La Roche liable and awarded Thomas one million dollars in damages.<sup>279</sup> However, the Federal District Court for the Northern District of Mississippi determined that as a matter of law, this verdict was not supported by the evidence.<sup>280</sup> Although the plaintiff presented expert testimony that the warning accompanying Accutane was inadequate and that an adequate warning would have prevented her injury, the Court asserted that this testimony was insufficient to support a jury conclusion that the allegedly inadequate warning caused the plaintiff's injuries, because it was not shown that an adequate warning would have convinced the prescribing physician, Dr. Meyer,

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<sup>272</sup> *Thomas*, 731 F. Supp. at 224.

<sup>273</sup> AMERICAN LAW OF PRODUCTS LIABILITY 3D, §89:65 Isotretinoin and Related Drugs

<sup>274</sup> *Thomas*, 731 F. Supp. at 226.

<sup>275</sup> Moser, *supra* note 258 at 240. "At trial, Thomas presented the testimony of Dr. O'Donnell to support her position that the warning accompanying Accutane was inadequate and that an adequate warning would have prevented her injury. Dr. O'Donnell testified that the warning given by Hoffman-La Roche was inadequate for two reasons. First, Hoffman-La Roche should have warned of the possibility of a slight risk of seizures associated with the use of Accutane in the fall of 1983, instead of in the spring of 1984. Second, because of the overall level of risk associated with Accutane, the warning should have stated that use of the product is contraindicated for all patients other than those with severe cystic acne." *Thomas*, 949 F.2d at 810.

<sup>276</sup> Moser, *supra* note 263 at 240.

<sup>277</sup> *Id.*

<sup>278</sup> *Id.*

<sup>279</sup> *Id.*

<sup>280</sup> *Id.*

not to prescribe Accutane for Ms. Thomas.<sup>281</sup> The Court emphasized that there was undisputable evidence that even after Hoffman-La Roche disclosed the available information on seizures to physicians, physicians continued to prescribe Accutane for hundreds of thousands of patients in the same way as before.<sup>282</sup> Furthermore, the Court stated that there was no evidence that a physician would change his or her behavior on the basis of warning not to prescribe Accutane to certain individuals.<sup>283</sup> In fact, in full knowledge of the incidence of seizures in a small number of Accutane users, the FDA did not consider Accutane so risky that such a warning was deemed necessary.<sup>284</sup> Therefore, with these findings with all favorable inferences in the light most favorable to the plaintiff, the trial court entered a judgment notwithstanding the verdict.<sup>285</sup> Consequently, the jury verdict was reversed and Hoffman-La Roche was relieved of the one million dollar judgment levied against it by the jury.<sup>286</sup> Upon this judgment, the plaintiff then appealed this decision to the 5<sup>th</sup> Circuit.<sup>287</sup>

The 5<sup>th</sup> Circuit addressed two issues: first, whether Hoffman-La Roche's conduct constituted a breach of duty to warn, and second, whether the absence of a warning on Accutane caused harm to the plaintiff.<sup>288</sup> In determining whether a breach of duty to warn occurred, the court applied the learned intermediary doctrine.<sup>289</sup> Under this doctrine, the manufacturer's failure to warn the patient of a product's risks does not render the product defective or unreasonably dangerous so long as the manufacturer adequately warns

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<sup>281</sup>AMERICAN LAW OF PRODUCTS LIABILITY 3D, *supra* note 273. "To satisfy the burden of establishing warning causation, a plaintiff may introduce either objective evidence of how a reasonable physician would have responded to an adequate warning, or subjective evidence of how the treating physician would have responded. But to create a jury question, the evidence introduced must be of sufficient weight to establish, by the preponderance of the evidence, at least some reasonable likelihood that an adequate warning would have prevented the plaintiff from receiving the drug." *Thomas*, 949 F.2d at 812.

<sup>282</sup>AMERICAN LAW OF PRODUCTS LIABILITY 3D, *supra* note 273.

<sup>283</sup>*Id.*

<sup>284</sup>*Id.*

<sup>285</sup>*Thomas*, 731 F. Supp. at 231.

<sup>286</sup>*Moser*, *supra* note 263.

<sup>287</sup>The citation to this case is 949 F.2d 806. The opinion was written by Circuit Judge Wisdom of the 5<sup>th</sup> Circuit. The Court applied Mississippi state law.

<sup>288</sup>*Moser*, *supra* note 263.

<sup>289</sup>*Moser*, *supra* note 263. Under Mississippi law, a product may be unreasonably dangerous if the manufacturer fails to warn of a non-obvious risk associate with the normal use of the product. When the product in question is a prescription drug, Mississippi follows the learned intermediary doctrine. *Thomas*, 949 F.2d at 811.

the learned intermediary, in this case the physician.<sup>290</sup> The physicians are then responsible for informing their patients of possible adverse reactions.<sup>291</sup> Under this doctrine, the 5<sup>th</sup> Circuit found that Hoffman-La Roche had no duty to inform the plaintiff directly of Accutane's possible side effects.<sup>292</sup> The court held that Hoffman-La Roche's only obligation was to provide Dr. Meyer with a *reasonable* warning of Accutane's possible side effects.<sup>293</sup> Considering the uncertainty of whether Accutane caused seizures in conjunction with Hoffman-La Roche's "Dear Doctor" letter, the 5<sup>th</sup> Circuit found that a reasonable warning was issued.<sup>294</sup> To resolve the question of whether Hoffman-La Roche's failure to issue a warning caused harm to the plaintiff, the 5<sup>th</sup> Circuit adopted a two-pronged test.<sup>295</sup> First, the plaintiff had to prove that had Hoffman-La Roche adequately informed Dr. Meyer of the risk of seizures associated with Accutane, he would not have prescribed this treatment for her.<sup>296</sup> Second, the plaintiff would have to establish that had Dr. Meyer not prescribed Accutane, she would not have been harmed.<sup>297</sup> The Court found that the first prong of this test had not been met, and therefore it was unnecessary to reach the question of whether Accutane caused Ms. Thomas' seizures.<sup>298</sup> The Circuit reached its finding primarily based upon the district court testimony of Dr. Meyer that he would have prescribed Accutane even if he had been warned directly from the manufacturer about the risk of seizures.<sup>299</sup> Additionally, the plaintiff had not established that a seizure warning would generally keep physicians from prescribing Accutane.<sup>300</sup>

The 5<sup>th</sup> Circuit essentially addressed two crucial questions in their review of this judgment: (1) "Is the reasonableness of a manufacturer's conduct relevant when deciding whether that manufacturer breached its duty

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<sup>290</sup> *Id.*

<sup>291</sup> Moser, *supra* note 263.

<sup>292</sup> *Id.*

<sup>293</sup> "Mississippi law requires a manufacturer to give a reasonable warning. To be reasonable, the warning should neither understate nor overstate the known risks associated with the use of a particular product." *Thomas*, 949 F.2d at 814.

<sup>294</sup> Moser, *supra* note 258.

<sup>295</sup> *Id.*

<sup>296</sup> *Thomas*, 949 F.2d at 812. *See also* Moser, *supra* note 263.

<sup>297</sup> *Thomas*, 949 F.2d at 814.

<sup>298</sup> Moser, *supra* note 263.

<sup>299</sup> *Id.*

<sup>300</sup> *Id.*

to warn?” and (2) “What is the proper criteria for ascertaining whether the manufacturer’s failure to warn was the proximate cause of an adverse drug reaction?”<sup>301</sup> In determining what the drug manufacturer’s duty to warn actually is, the 5<sup>th</sup> circuit rejected a strict liability standard and instead applied a reasonableness standard.<sup>302</sup> Under a reasonableness standard, the manufacturer must have acted negligently in order to be liable.<sup>303</sup> In a purely practical sense, the Court may have been ensuring the availability and accessibility to otherwise medically useful prescription drugs by not holding them strictly liable. Strict liability for the harmful side-effects of prescription drugs may increase the costs to the manufacturer, increase the costs to the consumer, and may ultimately, prevent such products from reaching the marketplace in the first place. One other distinguishing feature of this case and other cases dealing with drug manufacturers’ duty to warn is the attempt to articulate exactly how much risk must be present before a duty to warn arises.<sup>304</sup> Some courts have found that virtually any hint of danger warrants a warning.<sup>305</sup> Other courts, including the 5<sup>th</sup> Circuit in the Thomas case, require warnings for apparent dangers only.<sup>306</sup> The ten seizures reported at the time of Thomas qualify as a hint of danger, but the 5<sup>th</sup> Circuit did not hold the manufacturer of Accutane for not warning of these seizures.<sup>307</sup> In a sense, the 5<sup>th</sup> Circuit in Thomas used the reasonableness of Hoffman-La Roche’s conduct to justify their failure to warn of a non-apparent risk.<sup>308</sup> The 5<sup>th</sup> Circuit also required that an injured party prove that a warning would have prevented their physician from prescribing the drug that allegedly caused the harm.<sup>309</sup> If the Court finds that a warning would thus have not prevented the harm, the manufacturer is relieved of liability.<sup>310</sup> Manufacturers of prescription drugs must inform the medical community whenever there is danger and then the physician must determine

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<sup>301</sup> *Id.*

<sup>302</sup> *Id.*

<sup>303</sup> *Id.*

<sup>304</sup> *Id.*

<sup>305</sup> *Id.*

<sup>306</sup> *Id.*

<sup>307</sup> *Id.*

<sup>308</sup> *Id.*

<sup>309</sup> *Id.*

<sup>310</sup> *Id.*

whether prescribing the drug is in the best interest of the patient.<sup>311</sup>

Other cases addressed the issue of whether Hoffman-La Roche provided an adequate warning to consumers of Accutane. One such case is *Felix v. Hoffman La-Roche*<sup>312</sup> (Fla. 1989). This was an action to recover damages for birth defects that were allegedly caused by Hoffman-La Roche's failure to adequately warn that Accutane was dangerous for pregnant women.<sup>313</sup> The package insert warning stated that women of childbearing age should be instructed to use an effective form of contraception while taking Accutane.<sup>314</sup> The Court found that this warning was adequate as a matter of law because reasonable persons could only conclude that the warning clearly and unambiguously alerted physicians that Accutane should not be prescribed for pregnant women.<sup>315</sup> The Florida Supreme Court affirmed the findings of the trial court in favor of Hoffman-La Roche.<sup>316</sup> Other relevant and oft-cited cases addressing the issue of adequate warnings include *Wagner v. Roche Laboratories*<sup>317</sup> (1996), *Bealer v. Hoffman-La Roche* (1990)<sup>318</sup>, and *Hunt v. Hoffman La-Roche* (1992).<sup>319</sup>

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<sup>311</sup> *Id.* at 243-44.

<sup>312</sup> 540 So. 2d 102 (Fla. 1989).

<sup>313</sup> AMERICAN LAW OF PRODUCTS LIABILITY, *supra* note 273.

<sup>314</sup> *Id.*

<sup>315</sup> *Id.*

<sup>316</sup> *Id.*

<sup>317</sup> 671 N.E. 2d 252. A plaintiff brought a strict liability action against Roche, the manufacturer of Accutane, claiming that she contracted Pseudotumor Cerebri (PTC) as a result of her use of Accutane in combination with the antibiotic Minocin, both of which had been prescribed to treat a severe form of cystic acne. The plaintiff alleged that the manufacturer had failed to provide package insert warnings that Accutane could cause PTC and should not be used in conjunction with drugs such as Minocin. The appeals court found that the trial court had appropriately denied the manufacturer's motion for a directed verdict on the grounds that the evidence presented by the plaintiff was of sufficient probative value to create a jury question as to whether the manufacturer had failed to provide adequate warnings in light of the evidence and testimony. Importantly, the court found that the FDA's review, analysis, and approval of the warning language on the Accutane package insert did not insulate the manufacturer from liability on the inadequate warning claim. Additionally, despite FDA policy requiring that only information concerning known hazards should be included and warned about on package inserts, the manufacturer was not relieved from providing a warning of all potential adverse reactions which the manufacturer knew or should have known to exist at the time its product was marketed. *Id.* See also AMERICAN LAW OF PRODUCTS LIABILITY, *supra* note 273.

<sup>318</sup> 729 F. Supp. 43 (E.D. La. 1990). This was an action brought by a dermatologist's patient because of the therapeutic abortion she underwent on account of the high risk of birth defects associated with the ingestion of Accutane. Summary judgment was granted in favor of the manufacturer of Accutane because the manufacturers had sufficiently discharged their duty to warn the patient by providing the dermatologist with adequate information regarding the dangers and contraindications of Accutane. AMERICAN LAW OF PRODUCTS LIABILITY, *supra* note 273.

<sup>319</sup> 785 F. Supp. 547 (D. Md. 1992). This products liability action dealt with a child born with severe birth defects due to his mother's ingestion of Accutane during pregnancy. Summary judgment was granted to Hoffman-La Roche because both the mother and the prescribing physician were fully advised and aware of the danger of taking the drug during pregnancy. This decision affirmed the learned intermediary rule under Maryland law. AMERICAN LAW OF PRODUCTS LIABILITY *supra* note 273.

Most cases involving Accutane also have involved the manufacturer, Hoffman-La Roche as a defendant. But one important state case dealt not with the manufacturer's liability but with the liability of a physician or medical center for birth defects caused by Accutane use. On May 10<sup>th</sup>, 1996, the Supreme Court of Nevada heard the case of *Hogle v. Hall*<sup>320</sup>, reviewing a district court jury determination in favor of the plaintiff, Richard Hall, the father of the infant Bryce Michael Hall.

In 1986, Kim Hall, a 27 year old, began using Accutane to treat her severe acne upon the recommendation and prescription of her dermatologist.<sup>321</sup> On January 8<sup>th</sup>, 1991, she went to Dr. David Hogle for treatment of her acne.<sup>322</sup> Ms. Hall told Dr. Hogle that her last menstrual period had been that month.<sup>323</sup> Hogle then gave her a prescription for Accutane without following the checklist contained in the Physician's Desk reference.<sup>324</sup> He also did not give her any written warnings nor have her sign a written acknowledgment that she understood the risks of taking Accutane.<sup>325</sup> Ms. Hall became unknowingly pregnant on January 8, 1991, as her last menstrual period had actually been December 21, 1990.<sup>326</sup> She gave birth to a son, Bryce Michael Hall, on September 3, 1991, with severe birth defects.<sup>327</sup> He was profoundly retarded, his pupils do not respond to light, and he has virtually no ability to suck, swallow, or move his tongue or lower facial muscles.<sup>328</sup> It was also estimated that due to these severe defects, he may only live to ten or fifteen years of age.<sup>329</sup> Ms. Hall submitted a complaint of medical malpractice soon thereafter to the Northern Nevada Medical-Legal Screening Panel and in March of 1994, this panel returned a finding that there was a reason-

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<sup>320</sup>916 P.2d 814 (Nev. 1996).

<sup>321</sup>*Hogle*, 916 P.2d at 816.

<sup>322</sup>*Id.*

<sup>323</sup>*Id.*

<sup>324</sup>*Id.* This checklist appears in the Physician's Desk Reference and consists of six conditions that must be met by the patient before the physician prescribes Accutane. According to the guidelines, the patient must: (1) have severe disfiguring acne which has not responded to other therapies; (2) be reliable in carrying out and understanding instructions; (3) be capable of complying with mandatory contraceptive measures; (4) receive oral and written warnings of the teratogenic properties of Accutane and acknowledge understanding of these warnings in writing; (5) have a negative serum pregnancy test within two weeks prior to beginning Accutane; and (6) begin Accutane only on the second or third day of the next normal menstrual period. *Id.*

<sup>325</sup>*Id.* at 816.

<sup>326</sup>*Id.* at 816-17.

<sup>327</sup>*Id.* at 817.

<sup>328</sup>*Id.*

<sup>329</sup>*Id.*

able probability of medical malpractice by Hogle and that Bryce Hall was injured by such malpractice.<sup>330</sup> In March 1994, Richard Hall, Bryce's father, filed an initial complaint for the damages sustained by his son, naming Dr. Hogle and the Elko Regional Medical Center as defendants.<sup>331</sup> He sued for medical malpractice, alleging that the infant was born profoundly retarded because his mother took Accutane that Dr. Hogle had prescribed to her.<sup>332</sup> A six-day trial was held and a jury returned a verdict awarding the plaintiff \$2.63 million, finding the physician 60% negligent and the mother 40% negligent.<sup>333</sup> On appeal, Dr. Hogle and the Elko Regional Medical Center claimed that numerous procedural errors had occurred in this case and that the jury verdict should be overturned.<sup>334</sup> Instead, on May 10, 1996, the Nevada Supreme Court *affirmed* the \$2.6 million verdict, rejecting the contentions of the defendants.<sup>335</sup> In rejecting the defendants' procedural objections, the Court found that an unborn child who sustains injury prior to birth may sue under state law for those personal injuries after being born.<sup>336</sup> Under Nevada state law, the court said that the negligence of a parent cannot be imputed to an innocent child, and the proper remedy is for all tortfeasors to be held jointly and severally liable.<sup>337</sup>

This case is important because it seems to indicate that once the manufacturer has adequately printed warnings in Accutane's labeling, the physician is then legally responsible for ensuring that the patient understands the warning. Additionally, the patient does not escape liability either for her own actions. As the decision to take Accutane requires understanding of the risks by the manufacturer, prescribing physician, and the patient/consumer, the liability also can extend to all three of these parties. In the aforementioned

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<sup>330</sup> *Id.*

<sup>331</sup> *Id.*

<sup>332</sup> *Id.*

<sup>333</sup> *Id.*

<sup>334</sup> Hogle and the Elko Regional Medical Center cited numerous errors that occurred in the trial in an effort to get the verdict overturned. They argued that the trial court should not have allowed the substitution of Bryce's grandmother, Carol Evans, as guardian ad litem, because it was a fraudulent transfer. They also argued that an additur of \$300,000 assessed to Bryce Hall's damages, along with the assessment of attorney's fees subsequent to trial was improper. *Id.*

<sup>335</sup> *Id.* at 814.

<sup>336</sup> *Nevada Supreme Court Affirms \$2.6M Verdict Against Prescribing Physician*, PHARMACEUTICAL LITIG. REP. 11526 (August 1996).

<sup>337</sup> *Id.*

cases along with litigation relating to potential depressive and suicidal side effects, it seems clear that there are significant hurdles toward establishing any form of liability on the manufacturer. This is especially true considering active regulation by the FDA, which recognizes the overall effectiveness of this drug and need for this drug on the market.

There have been a number of recent cases concerning the link between Accutane use and suicide. Many cases have been resolved on procedural grounds.<sup>338</sup> However, the first jury trial over products liability claims that Accutane causes depression resulted in a defense verdict for Hoffman-La Roche.<sup>339</sup> Carla Gray of Ada, Oklahoma brought a lawsuit in August 2001 in the United States District Court for the Eastern District of Oklahoma, alleging that Accutane's manufacturer, Hoffman-La Roche, failed to provide adequate warnings about patients who experienced depression while taking Accutane.<sup>340</sup> Ms. Gray had begun taking Accutane in 1993 when she was 29. According to her attorney William Wilkinson, "she was a happily married mother of three children."<sup>341</sup> But after using Accutane for the next seven years, she spiraled into a "deep depression [that] destroyed her marriage and left her feeling continually 'hopeless and helpless.'"<sup>342</sup> Although Accutane's product package inserts mention depression as a possible side effect, the plaintiff asserted that it was relevant that this advisory was not included in the "boxed warnings section" of the package insert, which would have triggered concern by physicians.<sup>343</sup> The plaintiff sought over \$3 million in compensatory damages.<sup>344</sup>

On April 11<sup>th</sup>, after hearing five days of testimony, the jury returned a verdict for the defense.<sup>345</sup> Hoffman-La

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<sup>338</sup>For example, *Ohse v. Hoffman-La Roche*, 2002 WL 171989 (N.D. Ill.) was a suit brought against Hoffman-La Roche by plaintiff William Ohse for wrongful death for damages allegedly suffered by Ohse's son. Ohse claimed a link between his son's suicide and his son's use of Accutane. However, the action was dismissed without prejudice as requested by the plaintiff in order to add the prescribing physician to the suit, which would have destroyed diversity in this federal case.

<sup>339</sup>Margaret Cronin Fisk, *Suits Probe Acne Drug, Depression*, NAT'L L.J., pg. A4 (April 22, 2002).

<sup>340</sup>"Roche Wins Accutane Trial: Woman's Claim of Drug-Related Depression Rejected by Jury," Roche Press Release, April 16, 2002 available at [www.rocheusa.com/newsroom/current/2002/pr2002041601.html](http://www.rocheusa.com/newsroom/current/2002/pr2002041601.html)

<sup>341</sup>Fisk, *supra* note 339.

<sup>342</sup>*Id.*

<sup>343</sup>*Id.*

<sup>344</sup>*Id.*

<sup>345</sup>Roche Press Release, *supra* note 340.

Roche asserted that the jury's verdict was caused by a lack of scientific evidence.<sup>346</sup> A Roche press release on this trial states, "In the 20 years that Accutane has been available to patients with severe recalcitrant nodular acne, there has been no scientific evidence that shows that Accutane causes depression, despite numerous studies."<sup>347</sup> Defense counsel asserted, "Even the plaintiff's own experts had to admit that the theory that Accutane can cause depression is not accepted in the scientific community."<sup>348</sup> The plaintiff's attorney, William Wilkinson, blamed the jury's verdict on the timing of jury deliberations and the court's refusal to admit certain evidence.<sup>349</sup>

Plaintiff's attorneys in other depression-related lawsuits against Hoffman-La Roche contend that this defense victory will have no impact on the prospects of other claims.<sup>350</sup> One attorney who specializes in Accutane related cases called this case an "aberration" because the plaintiff did not have access to the "reams and reams" of documents purportedly showing a "direct link" between Accutane and dramatic psychological changes such as depression.<sup>351</sup> It is unlikely that this jury verdict will deter future Accutane related litigation considering the recent publicity around the possible connection between Accutane and depression.

In fact, as mentioned earlier, the family of Florida teen-ager Charles Bishop, who flew a stolen plane into a Tampa office tower, recently filed a \$70 million wrongful death and negligence lawsuit against Hoffman-La Roche in April 2002.<sup>352</sup> The lawsuit claims that Hoffman-La Roche negligently made an unsafe product that can cause psychosis, depression, and suicide and failed to adequately warn patients about these side

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<sup>346</sup>Fisk, *supra* note 339.

<sup>347</sup>Roche Press Release, *supra* note 340. In this press release, Dr. Douglas Jacobs, a Harvard physician specializing in suicide who testified in this case was quoted as saying, "Depression is a complex disease that is typically associated with multiple risk factors. The illness is often cyclical – that is, people can go in and out of states of depression and exhibit a range of symptoms that can be related to negative life events." *Id.*

<sup>348</sup>Defense Counsel for Hoffman-La Roche was Harry Woods of Crowe and Dunlevy from Oklahoma City, Oklahoma. Fisk, *supra* note 339.

<sup>349</sup>*Id.* The case closed on April 5, but the court recessed until April 11, when the jury returned to the court and began deliberating. Wilkinson asserted that this delay, in part, led to the defense verdict. He said, "in my opinion, the jurors had forgotten important information." *Id.*

<sup>350</sup>*Id.*

<sup>351</sup>This statement was made by plaintiffs' attorney Peter J. McNulty of Los Angeles' McNulty Law Firm, which specializes in Accutane related litigation. Fisk, *supra* note 339.

<sup>352</sup>"Accutane Acne Drug Maker Sued Over Suicide," USA TODAY, 4/16/02 available at <http://www.usatoday.com/money/health/2002-04-16-accutane-suicide.htm>.

effects.<sup>353</sup> The wrongful death element of the suit contends that Hoffman-La Roche manufactured an unsafe product, issued ineffective warnings, and underreported an alleged link between depression and suicide in its marketing, sale, and distribution of Accutane.<sup>354</sup> It alleged that Accutane caused Bishop to suffer a severe psychotic break with reality that resulted in his death.<sup>355</sup>

## VII. CONCLUSION: CAN THE ACCUTANE CONTROVERSY BE RESOLVED?

All of the health risks and dangers associated with the side-effects of Accutane use articulated in this paper remain serious concerns despite good faith efforts by both the FDA and the manufacturer of Accutane, Roche, to increase consumer and physician awareness of these risks. In fact, the recent approval of a generic form of this drug and continued television and print advertising indicates that consumer access to Accutane will continue to increase. Physicians are prescribing Accutane not only for the most severe forms of acne, but also for milder forms of acne due to patient request, deriving from the overall effectiveness of the drug. Additionally, there has been increased access to Accutane through the growth of prescription drug sales on the internet. Internet sales of Accutane pose a significant health risk due to the fact that obtaining this drug on foreign websites can allow patients to completely bypass the risk management requirements for Accutane.<sup>356</sup> Accutane obtained through foreign websites may generally be an unapproved version of the drug.<sup>357</sup> The FDA has taken a number of precautionary measures, but the internet sales still do represent

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<sup>353</sup> *Id.*

<sup>354</sup> “Family of Suicidal Pilot Files \$70M Suit Against Maker of Accutane,” PHARMACEUTICAL LITIG. REP. 3, (May 2002).

<sup>355</sup> *Supra* note 352.

<sup>356</sup> Woodcock, *supra* note 16.

<sup>357</sup> *Id.*

another factor that contributes to the foreseeable growth of Accutane use in the United States.<sup>358</sup>

The crucial tension visible in the controversy over Accutane use and regulation is the balancing between the public need for access to effective drugs with the risks associated with their use.<sup>359</sup> Accutane is seen as a “unique” treatment for people with the severest form of “nodular cystic acne,” which normally leaves deep scars. The justification was that for the most extreme cases of acne, a certain amount of risk, even teratogenicity, was acceptable. But this risk-benefit analysis has become somewhat more uncertain and imbalanced due to the increasing use of the drug for less severe cases of acne and the possibility of a link to depression and suicidal thoughts.

One major problem is that tracking of adverse events is poor and it is difficult to estimate how many individuals have been harmfully affected through Accutane use. One reason for this is that the FDA’s record keeping on adverse drug events is not entirely accurate. The agency estimates that it hears about only 10 percent of all bad outcomes.<sup>360</sup> Since Roche’s record keeping is also incomplete, there’s no way of knowing exactly how many infants must have been born with birth defects since Accutane was first marketed.<sup>361</sup> The conservative estimate is 160 such births.<sup>362</sup> Another reason for this uncertainty is that a large number of pregnancies incurred while under Accutane treatment are medically aborted and therefore go unreported.<sup>363</sup> Another problem with how Accutane is currently regulated is the emphasis on “labeling” as a precautionary measure for depressive side effects. The FDA has required changes to Accutane labeling to include full warnings about the danger of suicide, suicidal ideation, and depression associated with Accutane use.

Roche has complied with these requirements. Although this increases the amount of information available

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<sup>358</sup>The FDA has posted a special alert on its homepage warning consumers that Accutane should not be purchased over the internet. The FDA has also put Accutane on Import Alert, informing the Agency’s import inspectors that shipments of this drug are not appropriate for admission into the United States under FDA’s Personal Importation Policy. The FDA and Roche also have identified a number of websites that sell Accutane without a prescription and pursuing appropriate enforcement action.  
*Id.*

<sup>359</sup>Bull, *supra* note 88.

<sup>360</sup>Rafshoon, *supra* note 9.

<sup>361</sup>*Id.*

<sup>362</sup>*Id.*

<sup>363</sup>*Id.*

to physicians and consumers, improvements in labeling are limited in their effectiveness preventing suicide. As mentioned earlier, increasing the availability of information about these potential psychiatric side effects can allow patients who are especially susceptible to depression to choose alternative means of treatment. A certain population of potential consumers who may be naturally more inclined toward suicidal ideation can “screen” themselves from using Accutane. However, it seems that much of the anecdotal “evidence” of suicides linked to Accutane are of individuals who never had depressive tendencies nor exhibited psychological problems prior to beginning Accutane treatment.<sup>364</sup> To these individuals, increasing the amount of information available in the labeling will have little or no effect. If Accutane actually is causing suicide in some users, the FDA and manufacturer’s emphasis on improving the labeling will not solve this problem. In fact, improving the labeling of Accutane serves a more self-interested purpose for Roche. By including the potential psychological side effects of Accutane use in the labeling, Roche is protecting itself from liability for failure to warn when adverse events do occur rather than improving the safety of the product.<sup>365</sup> Therefore, the FDA cannot rely on labeling as their primary means of preventing the potentially dangerous side effects of Accutane.

There are other major concerns that contribute to the controversy over the use of Accutane. These concerns include a lack of mandatory controls, increased use by individuals with mild or moderate acne, and a general failure to employ the general precautions encouraged in the Accutane packaging and labeling. Also, a lack of conclusive scientific findings about these dangerous side effects also contributes to the uncertainty

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<sup>364</sup>“Our son BJ [Stupak] loved life. He was involved in sports, many school activities, treasurer of the student body, and President-elect of the student council at Menominee High School in Menominee, Michigan. BJ had many friends. He was a happy teenager who had great potential for life. He showed no signs of depression or loss of enthusiasm for life.” Rep. Bart Stupak, *supra* note 192. “Clay [Jackson] was not a depressed teenager, he was full of life. . . The two things that Clay loved doing more than anything, livestock shows and playing baseball, were just about to begin, the first stock show was scheduled for the day after he died. Clay didn’t have time to be depressed there was too much of life yet to experience and too many dreams left unfulfilled. . . I have to wonder what if I had taken the investigating officer in Clay’s death more seriously and looked into his suspicions about whether the drug Accutane has something to do with Clay’s death.” *Accutane – Is This Acne Drug Treatment Linked to Depression and Suicide: Hearing Before the House Comm. on Committee on Government Reform*, 106<sup>th</sup> Cong 32, 35 (December 5, 2000)( testimony of Charles H. “Stoney” Jackson, Jr., father of Clay Jackson). *See also* Fisk, *supra* note 339.

<sup>365</sup>Falsetti, *supra* note 238.

surrounding Accutane use. Many individuals are able to use Accutane safely without fear of the potential side effects.

One suggested yet impractical solution to the controversy over Accutane is to remove Accutane from the market altogether. The argument would be that the teratogenic qualities of the drug coupled with increasing anecdotal and circumstantial evidence of a link with depression have shifted the cost-benefit analysis so drastically that the costs now outweigh the benefits of the drug. This reasoning is also amplified by the fact that the population of Accutane users is increasing rapidly and therefore the number of individuals potentially exposed to the harmful side effects is also increasing. However, neither the FDA nor Roche have ever suggested removing Accutane from the market. Roche clearly has monetary interests at stake, since Accutane is a growing brand with no other real competitors with a built in consumer base. There will always be teenagers and increasingly, adults, who are struggling with acne. The FDA has never suggested a removal of Accutane from the market, instead choosing to increase educational efforts and regulating the sale, prescription, and distribution of Accutane. Lastly, the consumer demand is very high, as can be observed by the increasing number of individuals using Accutane. A representative of Roche states that if controls are as strict as those used for thalidomide, many women could be forced to go “underground,” either borrowing pills from their friends or purchasing drugs off the internet, which is far less safe than going through a physician.<sup>366</sup>

Another suggestion to increase the safety and resolve the controversy surrounding Accutane treatments is for the FDA to enact strict controls over who can prescribe or consume Accutane. For instance, the FDA took the controversial step in 1998 of permitting US sales of Thalidomide for leprosy patients.<sup>367</sup> This is the same sedative that caused thousands of European children to be born with missing limbs and other birth defects in the 1950’s and ‘60’s.<sup>368</sup> In fact, the Thalidomide tragedy was responsible for encouraging many of the FDA new drug procedures that are still necessary today. When the FDA permitted the sale of

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<sup>366</sup> *Id.*

<sup>367</sup> *Id.*

<sup>368</sup> *Id.*

Thalidomide, it also mandated a strict distribution system. The FDA permits only agency-approved physicians and pharmacies to dispense the drug, and patients must submit to a monthly survey to assure that they are using the medication properly.<sup>369</sup> The manufacturer of the drug also keeps track of every pill that leaves its warehouse.<sup>370</sup> However, this more stringent regulatory model is not near implementation at all. Although Accutane is teratogenic, it has never had the stigma associated with Thalidomide. Thalidomide caused an international medical crisis, whereas the overall harmful impact of Accutane has been more muted and understated. This may be the result of an increase in abortions rather than births with birth defects, porous record keeping, and the fact that many of the studies conducted about the dangerous side effects of Accutane use, especially in regard to psychological side effects, have been inconclusive. Roche has also balked at restrictions on the sale of Accutane.<sup>371</sup> Consequently, the FDA has taken a strong educational approach, gearing toward improving labeling and patient and physician information in order to improve the safety of Accutane use. Improving the education around the potential depressive side effects of Accutane may allow patients prone to depressive symptoms to “self-select” themselves out of these treatments, in favor of alternative treatments. Physicians, equipped with current information, may also play an important role in identifying patients who may be inclined toward psychological side effects and steering them away from Accutane. Roche in turn, has taken the proactive approach of engaging in its own educational efforts. Of course, these actions are blatantly self-interested. Pre-emptive self-regulation allows Roche to avoid potential FDA regulation, which may be exceedingly strict and inflexible and therefore more costly. Also, preventing adverse events also prevents negative publicity allowing Roche to increase its market sale and increase sales. But self-interest is not such a bad thing in this case – these incentives coincide conveniently with overall public health concerns for decreasing the overall incidence of harmful Accutane related side effects.

Another potential solution is to increase the number of mandatory controls imposed on physicians and con-

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<sup>369</sup> *Id.*

<sup>370</sup> *Id.*

<sup>371</sup> *Id.*

sumers. One commentator would like the FDA to require all doctors who prescribe Accutane, all pharmacists who dispense it, and all patients who take it to register with the FDA.<sup>372</sup> This is the same approach that the FDA takes with Thalidomide.<sup>373</sup> The FDA could also require that certain voluntary reporting measures or consent forms become mandatory before a prescription can be refilled. Unfortunately, such regulations may be *too* intrusive considering the increasing use of Accutane and the fact that a far larger number use Accutane without experiencing harmful side effects than those who do experience such side effects. All prescription drugs involve some risk of dangerous side effects and forcing such stringent regulations on Accutane users and prescribing physicians may set an unwelcome precedent for other prescription drugs.

Ultimately, the best solution may be to simply to let market forces work on the manufacturer and physicians while maintaining the safety information available to the consumer. Currently, both the prescribing physician and the pharmacist both provide information to new patients beginning Accutane treatments. The labeling that is included with Accutane is relatively extensive, mentioning that birth defects and depression/suicidal ideation are potential side effects. But the factor that may have the greatest effect on improving informed and safe use of Accutane is the effects of litigation. As discussed earlier, Roche has been sued a number of times for tort claims associated with both birth defects and suicide. Roche has resolved nearly all of these cases in its favor. However, doctors, not drug companies, are the ones who have gotten sued and lost when something has gone wrong. *Hogle v. Hall*, examined earlier in this paper, is an example of such an occurrence.<sup>374</sup> Because liability has been found against the physician, rather than the manufacturer, these dermatologists are taking their own stringent measures to protect themselves and their patients. The physicians may be encouraged, under the threat of potential litigation, to voluntarily take more stringent

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<sup>372</sup>Duenwald, *supra* note 169.

<sup>373</sup>*Id.*

<sup>374</sup>*Supra* note 320. There are also a number of other similar verdicts. One example is the case of Mary Ellen and Rupert Hansen and their son, William. William was their adoptive son, with the biological mother a 14- year old patient on Accutane who lied to her dermatologist about her sexual activity. Although normal looking, William exhibited extreme behavioral problems. The Hansen family sued this dermatologist and was awarded a \$2.7 million verdict by an Atlanta jury. Rafshoon, *supra* note 9.

precautionary measures than normally required. It is in their interest to fulfill their duties to educate the patient and ensure that this patient does not get pregnant nor begins treatment if prone to the depressive side effects of Accutane use.

Lastly, the question remains: How much blame or responsibility is to be placed upon the patient (consumer) of Accutane? The labeling of Accutane and the included Medical Guide details all potential side effects, including depression which has not even been conclusively linked to Accutane use. Both physicians and pharmacists are available to provide oral and written information on the dangers of beginning Accutane treatments. If a patient simply reads this enclosed information, that patient should understand the potential dangers of Accutane treatment and act accordingly. Unfortunately, the reality is that many Accutane users do not take adequate precautions to prevent harmful side effects. One study found that more than one-third of female Accutane users surveyed didn't use any birth control.<sup>375</sup> Many never waited to start taking Accutane before they or their doctors were sure they were not pregnant.<sup>376</sup> As for the potential psychological side effects, patients must understand these warnings and consult their physician if they start feeling depressive symptoms. Ultimately, the responsibility must lie with the patient when all the educational responsibilities of the manufacturer and prescribing physician are fulfilled.

Dealing with the Accutane controversy must be a joint effort with the manufacturer, prescribing physicians, and the consumer. The number of acne sufferers using Accutane will continue to increase. Consumer demand for Accutane is increasing as is the availability of Accutane, due to the introduction of generic versions, an increase in advertising, and the increasing use of the internet for prescription drug sales. This increase in Accutane use and the increase in the population potentially exposed to dangerous side effects necessitates

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<sup>375</sup>This study was conducted by the Slone Epidemiology Center, affiliated with the Boston University medical and public health schools. Slone has been heavily involved in Roche's risk management program for Accutane since it was instituted in 1989 as part of a deal the company agreed to with the FDA. The center has been responsible for overseeing the survey that serves as a benchmark for Roche to measure compliance with its pregnancy prevention efforts. Participation in this survey is voluntary, with most women in the survey responding to a form included in their package of Accutane pills. Data from Slone showed that nearly all women knew that they should not become pregnant on Accutane. However, more than one-third of those surveyed did not use any birth control. *Id.*

<sup>376</sup>*Id.*

further study and continued regulation and oversight by the FDA. But study alone takes time and may ultimately be inconclusive. Neither the FDA nor Roche seems inclined to impose more stringent regulations on either manufacturing or on prescribing physicians. One FDA representative stated that the “FDA does not regulate the practice of medicine,” and neither the drug company nor the government intends to get involved in doctors’ prescribing habits.<sup>377</sup> So ultimately, improved and constantly updated patient education and normal market incentives may be the only means of ensuring that adverse events, both natal and psychological, steadily decrease. But is this all really worth it for clearer skin? This is the assumption underlying this entire controversy that has yet to be fully considered.

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<sup>377</sup> *Id.*