

# Incentivizing Postmarketing Pharmaceutical Product Safety Testing with Extension of Exclusivity Periods

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## INTRODUCTION

Recent withdrawal of Food and Drug Administration (“FDA”) approved drugs from the market, increased safety warnings of FDA-approved drugs, and highly publicized pharmaceutical products liability litigation have drawn attention to the mechanism by which the FDA and pharmaceutical manufacturers evaluate the safety of FDA-approved drugs. A report from the Institute of Medicine<sup>1</sup> suggests the FDA has not effectively monitored the safety of pharmaceuticals subsequent to initial approval for use and recommends changes to the process by which the FDA monitors postmarketing-adverse-event-surveillance. The congressional response, the Food and Drug Administration Amendments Act of 2007,<sup>2</sup> enhances the ability of the FDA to implement a plan for periodic postmarket evaluation of pharmaceuticals and enforce the obligation of manufacturers to perform FDA-requested postmarket safety studies via penalties or fines.<sup>3</sup> This plan, however, fails to provide incentives for pharmaceutical manufacturers to employ important ongoing postmarket safety evaluation of their drugs.

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<sup>1</sup> COMM. ON THE ASSESSMENT OF THE US DRUG SAFETY SYS., INST. OF MED. OF THE NAT’L ACADS., *THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC* (Alina Baciu, Kathleen Stratton, Sheila P. Burke, eds., 2007) [hereinafter *THE FUTURE OF DRUG SAFETY*].

<sup>2</sup> Food and Drug Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.).

<sup>3</sup> 21 U.S.C. § 333(f)(4)(A)(ii) (Supp. 2007).

Like other businesses, the pharmaceutical industry is driven by the profit motive.<sup>4</sup> Profitability of pharmaceutical companies is dependent on balancing the costs of identifying, developing, patenting, testing and obtaining approval to market a new drug with the ability to market the drug at a reasonable price during the patent term.<sup>5</sup> In part because the industry generates huge profits,<sup>6</sup> it has been severely criticized for focusing on profitability at the expense of the consumer<sup>7</sup>—in terms of both price protection<sup>8</sup> and safety. Nonetheless, the pharmaceutical industry is, in fact, an economic enterprise driven by maximization of profits.<sup>9</sup> Consequently, postmarket safety evaluation of pharmaceuticals must be profitable in order to ensure compliance.

This Note proposes a promising mechanism of ensuring more crucial postmarket safety evaluations of pharmaceuticals by extending the exclusive marketing period—normally limited to the patent term—as a reward.<sup>10</sup> Extending the exclusivity period has been demonstrated to be an effective incentive for pharmaceutical manufacturers to perform additional studies,<sup>11</sup> while having no impact on the timing of the initial FDA approval for marketing.<sup>12</sup> The expense of post-approval testing is likely to be balanced by ample earnings during the reward period, making the choice of performing such testing economically attractive. In addition, the benefit to consumers resulting from the increase in safety of marketed pharmaceuticals counteracts any negative financial

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<sup>4</sup> See Richard A. Epstein, *What's Good for Pharma is Good for America*, BOSTON GLOBE, Dec. 3, 2006, available at [http://www.boston.com/news/globe/ideas/articles/2006/12/03/whats\\_good\\_for\\_pharma\\_is\\_good\\_for\\_america](http://www.boston.com/news/globe/ideas/articles/2006/12/03/whats_good_for_pharma_is_good_for_america).

<sup>5</sup> See *id.*

<sup>6</sup> The pharmaceutical industry generates about \$250 billion in revenue. See *id.*

<sup>7</sup> See generally MARCIA ANGELL, *THE TRUTH ABOUT THE DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT* (2005).

<sup>8</sup> Americans spent more than \$200 billion on prescription drugs over the past year. See IMS Health, <http://www.imshealth.com/ims/portal/pages/homeFlash/us/0,2764,6599,00.html> (last visited Feb. 11, 2008) (providing statistics on retail pharmaceutical sales, updated monthly).

<sup>9</sup> See Epstein, *supra* note 4.

<sup>10</sup> See *infra* Part III.A.

<sup>11</sup> See *infra* Part III.B.

<sup>12</sup> Since the extension period and the additional studies would occur after the drug has been FDA approved, it would have no effect on the timing of initial FDA approval for marketing.

impact on consumers that extended exclusivity may cause.<sup>13</sup> Moreover, market exclusivity applied to marketed products stimulates further innovation and development of those and related products, resulting in a general benefit to the health of the population.<sup>14</sup>

Part I of this Note discusses the problem of drugs reaching the market with undiscovered, but discoverable, risks that result in harm to consumers. Part II of this Note explains how the economic structure of the pharmaceutical industry, including the regulatory system, protection of the patent monopoly and anticipation of liability, provides disincentive for further safety testing of pharmaceuticals. Part III puts forth a proposal to incentivize post-approval safety testing of pharmaceuticals by extending the period of market exclusivity. Implementation of this proposal should result in increased knowledge of the risks of marketed pharmaceuticals, improving the safety of these products.

#### I. DEFECTIVE DRUGS REACH THE MARKET RESULTING IN HARM

Extensive safety and efficacy testing is required in order for a pharmaceutical to obtain FDA approval for marketing.<sup>15</sup> Nonetheless, adverse drug reactions<sup>16</sup> revealed subsequent to FDA

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<sup>13</sup> The financial impact on consumers, resulting from extending the exclusivity period, would have to be balanced against the value of increased safety of marketed pharmaceuticals resulting from the additional studies in order to determine an optimal length of time for the reward. Balancing of these factors is not the subject of this Note.

<sup>14</sup> See Gregory J. Glover, *The Influence of Market Exclusivity on Drug Availability and Medical Innovations*, 9 AM. ASS'N PHARMACEUTICAL SCI. J. E312, E315 (2007) ("IP rights extended to final, marketable drug products make further, related innovation possible. . . . IP protection of a marketable drug product encourages not only development of that product but further development of related innovations to expand and improve therapies and cures.").

<sup>15</sup> See Michelle Meadows, *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, 36 FDA CONSUMER 19 (2002), available at [http://www.fda.gov/Fdac/features/2002/402\\_drug.html](http://www.fda.gov/Fdac/features/2002/402_drug.html) (briefly outlining the FDA approval process); see also 21 C.F.R. § 314 (2008) (providing the federal regulations for new drug approval).

<sup>16</sup> An adverse drug reaction is "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man." WORLD HEALTH ORG., SAFETY OF MEDICINES: A GUIDE TO DETECTING AND REPORTING ADVERSE DRUG REACTIONS, WHY HEALTH PROFESSIONALS NEED TO TAKE ACTION 5 (2002), available at [http://whqlibdoc.who.int/hq/2002/WHO\\_EDM\\_QSM\\_2002.2.pdf](http://whqlibdoc.who.int/hq/2002/WHO_EDM_QSM_2002.2.pdf). Adverse drug events

approval and products liability suits demonstrate that pharmaceuticals approved for marketing may cause harm to their users. Incentivizing pharmaceutical manufacturers to perform postmarket safety research would result in increased knowledge of those risks, which may be included in improved warning labels, thereby enhancing the safety of marketed pharmaceuticals.

Part A of this section discusses why the current method of evaluating the safety of drugs approved for marketing is inadequate to maximize their safety. Part B provides examples of marketed pharmaceuticals that had serious risks that would have been discoverable through well-designed postmarket studies.

#### A. *Current Safety Testing of Pharmaceuticals is Inadequate*

Although the FDA is charged with implementing procedures to maximize the safety of drugs approved for marketing,<sup>17</sup> the incidence of adverse drug events demonstrates that defective drugs reach the market, resulting in harm.<sup>18</sup> Drugs are found to be defective most frequently based on the criteria for failure to warn of risks associated with use rather than alternative theories of design or manufacturing defects.<sup>19</sup>

Generally, pharmaceutical manufacturers become aware of potential risks associated with use of a drug during clinical trials

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include adverse drug reactions and negative responses to drugs due to error. See Maria-Jose Otero, Alfonso Dominguez-Gil, Angel A. Bajo, & Jose A. Maderuelo, *Characteristics Associated with Ability to Prevent Adverse Drug Reactions in Hospitalized Patients—A Comment*, 19 PHARMACOTHERAPY 1185, 1185 (1999).

<sup>17</sup> See Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 393(b) (2000) (delineating the mission of the FDA); Meadows, *supra* note 15 (describing the procedures the FDA uses to maximize safety of drugs approved for marketing).

<sup>18</sup> See Catherine T. Struve, *The FDA and the Tort System: Postmarketing Surveillance, Compensation, and the Role of Litigation*, 5 YALE J. HEALTH POL'Y L. & ETHICS 587, 607 (2005) (discussing the FDA's inability to address all safety issues prior to products entering market); see also Janet Woodcock, Dir., Ctr. for Drug Evaluation and Research, *Medical Errors: Understanding Adverse Drug Events*, Address Before the Senate Committee on Health, Education, Labor, and Pensions (Feb. 1, 2000), available at <http://www.hhs.gov/asl/testify/t000201a.html> (indicating that some adverse drug reactions are due to undiscovered side effects not included in product labelling).

<sup>19</sup> LARS NOAH & BARBARA NOAH, *LAW, MEDICINE, AND MEDICAL TECHNOLOGY* 523 (2002).

conducted for the purpose of approval by the FDA.<sup>20</sup> These risks of drug use are included in the package inserts<sup>21</sup> and in information provided to the prescribing physicians. Although extensive research, including safety and efficacy studies, is required for FDA approval to market a pharmaceutical, the research is necessarily limited in size, scope and time.<sup>22</sup> Consequently, side effects occurring at low frequencies, due to longer duration of drug use, and occurring in particular subpopulations, are generally not discovered in the pre-approval period.<sup>23</sup> As a result, the actual extent of discoverable risks associated with an FDA-approved drug is not known and, therefore, not communicated to prescribing physicians or consumers.<sup>24</sup>

During the postmarketing period, adverse drug reactions<sup>25</sup> become more apparent due to the more widespread use of the drug over a longer period of time in a heterogeneous population.<sup>26</sup> The incidence of adverse drug reactions illustrates the extent of the problem. Adverse drug reactions ranked between the fourth and sixth leading cause of death in the United States<sup>27</sup> and comprise three percent of hospital admissions.<sup>28</sup> Among patients already

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<sup>20</sup> See Woodcock, *supra* note 18 (noting that more frequent adverse reactions are usually detected in clinical trials before drugs go on the market); Struve, *supra* note 18, at 587.

<sup>21</sup> See FDA, Drugs@FDA Instructions: Health Information, <http://www.fda.gov/cder/drugsatfda/instructionsHealth.htm> (last visited Oct. 26, 2008) (defining a "Patient Package Insert" as containing "information for patients on how to safely use a drug product" and a "part of the FDA-approved labeling").

<sup>22</sup> See THE FUTURE OF DRUG SAFETY, *supra* note 1, at 37–39.

<sup>23</sup> See Woodcock, *supra* note 18; Struve, *supra* note 18, at 597–99; see also William M. Sage, *Drug Product Liability and Health Care Delivery Systems*, 40 STAN. L. REV. 989, 990 (1988) (noting that adverse drug reactions may depend on individual chemistry of the patients and may not be revealed for years).

<sup>24</sup> The limited sample size and duration of pre-approval studies compromise the ability of the FDA to identify safety problems and to reveal low frequency adverse events. See THE FUTURE OF DRUG SAFETY, *supra* note 1, at 37.

<sup>25</sup> See *supra* note 16 (defining adverse drug reaction).

<sup>26</sup> See Woodcock, *supra* note 18; Struve *supra* note 18, at 597–99; see also Sage, *supra* note 23.

<sup>27</sup> See Jason Lazarou, Bruce H. Pomeranz & Paul N. Corey, *Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-analysis of Prospective Studies*, 279 J. AM. MED. ASS'N 1200, 1202 (1998) (citing data from 1994).

<sup>28</sup> Robert L. Kane, *Iatrogenesis: Just What the Doctor Ordered*, 5 J. COMMUNITY HEALTH 149, 150 (1980).

hospitalized, approximately one-third experience an adverse drug reaction.<sup>29</sup> The annual direct cost of managing adverse drug reactions of hospitalized adults is estimated to be between \$1.6 and \$4.2 billion.<sup>30</sup> Statistics are not available on adverse drug reactions that do not result in hospitalization.

Individual incidents of adverse drug reactions, revealed through continued use of approved drugs in the larger population over time via spontaneous physician or consumer reports, must be reported by the manufacturer to the FDA.<sup>31</sup> “This collection of voluntarily submitted case reports represents the weakest form of epidemiologic evidence . . . .”<sup>32</sup> The passive nature of the reporting requirement likely results in underreporting of the incidence of adverse events.<sup>33</sup> In addition, the cause of a reported adverse reaction to a drug is not necessarily revealed by individual incidents. Moreover, adverse drug reactions reported over a long time frame may fail to reveal a trend in the nature of these events and, rather than suggesting a systematic risk, appear idiosyncratic. The converse is also possible. That is, a collection of independent adverse events may appear to represent a risk of use of a drug even when there is no actual causation.

Nonetheless, analyses of these data by drug manufacturers and the FDA<sup>34</sup> sometimes result in changes to the package inserts, stronger label warnings, and withdrawal of drugs from the

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

<sup>30</sup> See D.C. Classen, S.L. Pestotnik, R.S. Evans, J.F. Lloyd & J.P. Burke, *Adverse Drug Events in Hospitalized Patients: Excess Length of Stay, Extra Costs, and Attributable Mortality*, 277 J. AM. MED. ASS'N 301 (1997).

<sup>31</sup> Postmarketing Reporting of Adverse Drug Experiences, 21 C.F.R. § 314.80(c) (2008); Other Postmarketing Reports, 21 C.F.R. § 314.81 (2008).

<sup>32</sup> Bruce M. Psaty & Sheila P. Burke, *Protecting the Health of the Public—Institute of Medicine Recommendations of Drug Safety*, 355 NEW ENG. J. MED. 1753, 1753 (2006).

<sup>33</sup> See Michael A. Friedman, *Science for Judges II: The Practice of Epidemiology and Administrative Agency Created Science: What is the Value of an FDA Approval in a Judicial Matter?*, 12 J.L. & POL'Y 559, 570–71 (2004) (suggesting ten percent or less of adverse drug events are reported). Considering that adverse drug events include overdosage and misprescription, as well as side effects, secondary effects and hypersensitivity, see Otero et al., *supra* note 25, adverse drug event reporting may be overinclusive, as well.

<sup>34</sup> Of concern is the dependence of the FDA on manufacturers for preapproval drug testing, postmarket data collection and reporting. See Sage, *supra* note 23, at 1020.

market.<sup>35</sup> Fifty-six of the 548 drugs approved by the FDA between 1975 and 1999 were either withdrawn from the market or required to include a black-box warning—the strictest warning label.<sup>36</sup> About four percent of drugs are eventually withdrawn from the market, and twenty percent of drugs get black-box warnings after approval.<sup>37</sup> However, without systematic postmarket research, pharmaceuticals may remain on the market lacking an appropriate warning of risks because those risks have not been revealed via spontaneous reporting. In addition, useful pharmaceuticals may be withdrawn from the market because the extent of risk is not correctly evaluated.<sup>38</sup> Of particular concern is that patients are harmed in the interval between initial FDA approval and changes to the package inserts or withdrawal of the drug from the market.

Data on post-approval adverse drug reactions suggest that intentional post-approval testing would likely reveal the same adverse effects earlier and, with planned studies, the data would be

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<sup>35</sup> See, e.g., FDA, FDA Announces Important Changes and Additional Warnings for COX-2 Selective and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), <http://www.fda.gov/CDER/Drug/advisory/COX2.htm> (last visited Oct. 26, 2008) (announcing FDA's request for withdrawal of Bextra and that all manufacturers of prescription NSAIDs revise their labeling and include more specific risk information in package inserts).

<sup>36</sup> See Karen E. Lasser, Paul D. Allen, Steffe J. Woolhandler, David U. Himmelstein, Sidney M. Wolfe & David H. Bor, *Timing of New Black Box Warnings and Withdrawals for Prescription Medications*, 287 J. AM. MED. ASS'N 2215, 2216 (2002).

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

<sup>38</sup> For example, Tysabri (natalizumab), a drug used to treat multiple sclerosis, was withdrawn from the market after it was associated with the development of usually fatal progressive multifocal leukoencephalopathy. Burt Adelman, Alfred Sandrock, & Michael A. Panzara, *Natalizumab and Progressive Multifocal Leukoencephalopathy*, 353 NEW ENG. J. MED. 432, 432 (2005). The data (three incidences in 3,116 patients treated over 17.9 months) revealed a risk of 65 fatalities per 100,000 person-years. Joshua T. Cohen & Peter J. Neumann, *What's More Dangerous, Your Aspirin or Your Car? Thinking Rationally About Drug Risks (and Benefits)*, 26 HEALTH AFF. 636 (2007). Because the risk is low and the drug is effective in mitigating the symptoms for many multiple sclerosis patients, the FDA reintroduced the drug in 2006, subject to closer risk management. See C. Sheridan, *Tysabri Back on Market*, 24 NATURE BIOTECHNOLOGY 874 (2006).

more reliable.<sup>39</sup> Postmarketing studies for new uses sometimes reveal side effects, which were not revealed via pre-approval studies.<sup>40</sup> However, the FDA does not routinely require additional postmarket research.<sup>41</sup> In fact, until recently,<sup>42</sup> with very few exceptions,<sup>43</sup> once a drug was approved, the FDA lacked the authority to require manufacturers to perform postmarketing studies, even those agreed to prior to approval.<sup>44</sup> Consequently, of the 1,259 postmarketing studies requested, less than 30 percent have been initiated.<sup>45</sup> While it is “impossible to design an absolutely safe drug,”<sup>46</sup> the safety of FDA-approved pharmaceuticals can be improved by focused research designed to reveal additional risks. One estimate suggests that up to eighty

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<sup>39</sup> For a comparison of the merits of different study designs see BETH DAWSON & ROBERT G. TRAPP, BASIC AND CLINICAL BIostatISTICS 19–21 (McGraw-Hill Professional, 2004).

<sup>40</sup> Vioxx, for example, was FDA-approved for treatment of pain and inflammation. A clinical trial to evaluate Vioxx for prevention of recurrent colon polyps revealed serious adverse cardiovascular effects. See Robert S. Bresalier, Robert S. Sandler, Hui Quan, James A. Bolognese, Bettina Oxenius, Devin Horgan, Christopher Lines, Robert Riddell, Dion Morton, Angel Lanas, Marvin A. Konstam, John A. Baron, for the Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators, *Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial*, 352 N. ENG. J. MED. 1092 (2005).

<sup>41</sup> See THE FUTURE OF DRUG SAFETY, *supra* note 1, at 156 (“[Ninety-one] percent of postmarketing commitments between 1990 and 2004 were requested by the agency rather than being required by statute or regulation”).

<sup>42</sup> The Food and Drug Administration Amendments Act of 2007 gives the FDA the authority to fine pharmaceutical manufacturers who fail to implement FDA-directed post-approval safety studies. See Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.).

<sup>43</sup> See Stephen J. Schanz, *Pharmaceutical Postmarket Review: Fact of Fiction*, 62 FOOD & DRUG L.J. 493, 494 (2007) (noting that the FDA can require a postmarketing study (1) to verify clinical benefits of drug approved via the accelerated process, (2) when a drug has been approved based only on animal studies, (3) for the purpose of marketing a drug for use in children, (4) to determine if there are grounds to revoke approval).

<sup>44</sup> See Psaty, *supra* note 32, at 1753.

<sup>45</sup> See Jerry Avorn, *Paying for Drug Approvals—Who’s Using Whom?*, 356 N. ENG. J. MED. 1697, 1698 (2007) (presenting data on the status of open commitments for postmarketing studies requested by the FDA, as of September 30, 2006, as reported in the Federal Register).

<sup>46</sup> Sage, *supra* note 23, at 990.

percent of adverse drug reactions could be predicted, most of which could be prevented by further study.<sup>47</sup>

The FDA primarily relies on analyses of adverse drug reactions over a long time frame to reveal additional risks of approved pharmaceuticals, even though such reactions are underreported and fail to establish causation.<sup>48</sup> As explained in the next section, systematic evaluation of pharmaceutical safety during the post-approval period would reveal risks earlier, and with greater confidence of accuracy, thereby reducing harm to patients.

*B. Some Risks of FDA-Approved Pharmaceuticals Are Discoverable by Postmarket Research*

A review of data on adverse drug reactions suggests that clinical studies performed with the purpose of evaluating the risk of some of those reactions would have revealed them earlier. The following are just a few examples of pharmaceuticals for which post-approval testing may have revealed important safety data.

Vioxx (rofecoxib), a product of Merck & Co., Inc., is a nonsteroidal anti-inflammatory drug (“NSAID”),<sup>49</sup> which was FDA-approved in 1999 to treat pain associated primarily with osteoarthritis.<sup>50</sup> Although there were early indications of serious adverse cardiovascular events associated with use of Vioxx, Merck asserted that the data was inconclusive.<sup>51</sup> Based on increased risk

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<sup>47</sup> See MILTON MORRIS SILVERMAN & PHILIP LEE, *PILLS, PROFITS AND POLITICS* 266 (University of California Press, 1974).

<sup>48</sup> See *supra* notes 31–37 and accompanying text.

<sup>49</sup> See Chronic Pain Medical Glossary, <http://www.pbs.org/secondopinion/episodes/chronicpain/medicalglossary/story425.html> (last visited Nov. 22, 2008) (defining NSAID as a “[c]lass of medication, which does not contain steroids, that is often used as the initial pharmacological therapy for common inflammation . . .”).

<sup>50</sup> See Letter from Dr. Robert J. DeLap to Dr. Robert E. Silverman (May 20, 1999) (on file with the Center for Drug Evaluation and Research, FDA), available at [http://www.fda.gov/cder/foi/nda/99/021042\\_52\\_vioxx\\_appltr.pdf](http://www.fda.gov/cder/foi/nda/99/021042_52_vioxx_appltr.pdf).

<sup>51</sup> See Claire Bombardier, Loren Laine, Alise Reicin, Deborah Shapiro, Ruben Burgos-Vargas, Barry Davis, Richard Day, Marcos Bosi Ferraz, Christopher J. Hawkey, Marc C. Hochberg, Tore K. Kvien, Thomas J. Schnitzer, for The VIGOR Study Group, *Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*, 343 N. ENGL. J. MED. 1520, 1523, 1526–27 (2000) (asserting that the apparent elevation in cardiovascular events with Vioxx use are consistent with a cardioprotective effect in the naproxen arm of the study).

of adverse cardiovascular events revealed during a study for a new use of the drug, Vioxx was voluntarily withdrawn from the market in 2004.<sup>52</sup> At about the same time, a study to determine the cancer prevention effects of Celebrex, Pfizer's competing drug in the same class, revealed similar cardiovascular risks.<sup>53</sup> "Many drug-safety researchers believe . . . that appropriately conducted studies would have revealed the cardiovascular toxicity of [Vioxx] well before the end of its 5-year run."<sup>54</sup> A centralized data network<sup>55</sup> could have detected a risk of serious cardiovascular events associated with Vioxx after less than three months, allowing for the recommendation of targeted follow-up research.<sup>56</sup>

With Rezulin (troglitazone), concerns about a risk of liver toxicity prior to FDA approval<sup>57</sup> might have suggested the need for post-approval safety research. Rezulin, a Warner-Lambert product, was FDA-approved in 1997 for the treatment of Type II diabetes.<sup>58</sup> Continued Rezulin use in over a million people revealed a high occurrence of acute liver toxicity amongst users.<sup>59</sup> In March 2000, the FDA requested that the manufacturer withdraw

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<sup>52</sup> See *FDA Issues Public Health Advisory on Vioxx as its Manufacturer Voluntarily Withdraws the Product*, FDA NEWS, Sept. 30, 2004, <http://www.fda.gov/bbs/topics/news/2004/NEW01122.html>.

<sup>53</sup> Memorandum from John K. Jenkins, Director, FDA Office of New Drugs, and Paul J. Seligman, Director, Office of Pharmacoepidemiology and Statistical Science, to NDA files 20-998, 21-156, 21-341, 21-042, at 4 (Apr. 6, 2005), available at <http://www.fda.gov/cder/drug/infopage/cox2/nsaiddecisionmemo.pdf>.

<sup>54</sup> Avorn, *supra* note 45, at 1699.

<sup>55</sup> This would be a mechanism of systematically collecting, collating, and analyzing adverse events associated with a drug in order to identify a potential risk which could be addressed by a postmarket study.

<sup>56</sup> Mark McClellan, *Drug Safety Reform at the FDA—Pendulum Swing or Systematic Improvement?*, 356 NEW ENG. J. MED. 1700, 1702 (2007) (citing R. Platt, *The Future of Drug Safety—Challenges for FDA*, Presentation at the Institute of Medicine Forum, Washington, DC (Mar. 12, 2007)).

<sup>57</sup> See *Rezulin to Be Withdrawn from the Market*, HHS NEWS, Mar. 21, 2000, <http://www.fda.gov/bbs/topics/NEWS/NEW00721.html>.

<sup>58</sup> See *Drug Approvals for August 1997* (Oct. 3, 1997), <http://www.fda.gov/cder/da/da0897.htm>.

<sup>59</sup> David Willman, *FDA Urged to Heed Warnings on Rezulin*, L.A. TIMES, May 23, 1999, at A4.

Rezulin from the market.<sup>60</sup> Focused postmarket clinical research conducted at the onset of FDA-approval could have saved lives.<sup>61</sup>

Unlike Vioxx or Rezulin, there were few concerns about the safety of Selective Serotonin Reuptake Inhibitors (“SSRIs”) when they first came on the market. SSRIs were thought to be a safer alternative to other classes of antidepressants.<sup>62</sup> SSRIs are a class of antidepressant drugs used to treat major depressive disorder (“MDD”) and other psychiatric disorders.<sup>63</sup> The first SSRI approved by the FDA in 1987 was Prozac (fluoxetine), manufactured by Eli Lilly.<sup>64</sup> By 1990, there was some indication that patients prescribed SSRIs were prone to suicidal ideation.<sup>65</sup> While there were a number of subsequent reports of suicidal ideation associated with SSRI use in depressed patients,<sup>66</sup> the

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<sup>60</sup> See *Rezulin to Be Withdrawn from the Market*, HHS NEWS, Mar. 21, 2000, <http://www.fda.gov/bbs/topics/NEWS/NEW00721.html>.

<sup>61</sup> See Holcomb B. Noble, *Removal of Diabetes Drug Meets with Mixed Feelings*, N.Y. TIMES, Mar. 28, 2000, at F7 (noting that sixty-three people had died from Rezulin use prior to the FDA’s request of withdrawal of Rezulin from the market).

<sup>62</sup> See, e.g., Gerald Gartlehner et al., *Comparative Benefits and Harms of Second-Generation Antidepressants: Background Paper for the American College of Physicians*, 149 ANNALS OF INTERNAL MED. 734, 734 (2008).

<sup>63</sup> See FDA Public Health Advisory, *Suicidality in Children and Adolescents Being Treated With Antidepressant Medications* (Oct. 15, 2004), <http://www.fda.gov/cder/drug/antidepressants/SSRIPHA200410.htm>.

<sup>64</sup> 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, 274 (2002). Other SSRIs include Zoloft (sertraline), Paxil (paroxetine), Luvox (fluvoxamine), Celexa (citalopram), and Lexapro (escitalopram oxalate). *Id.*

<sup>65</sup> See Martin H. Teicher, Carol Glod & Jonathan O. Cole, *Emergence of Intense Suicidal Preoccupation During Fluoxetine Treatment*, 147 AM. J. PSYCHIATRY 207, 207–10 (1990).

<sup>66</sup> See, e.g., Timothy D. Brewerton, *Fluoxetine-Induced Suicidality, Serotonin, and Seasonality*, 30 BIOLOGICAL PSYCHIATRY 190, 190–96 (1991); Guy Chouinard, *Fluoxetine and Preoccupation with Suicide*, 148 AM. J. PSYCHIATRY 1258, 1258–59 (1991); John Downs et al., *Preoccupation with Suicide in Patients Treated with Fluoxetine*, 148 AM. J. PSYCHIATRY 1090, 1090–91 (1991); Cynthia E. Hoover, *Additional Cases of Suicidal Ideation Associated with Fluoxetine*, 147 AM. J. PSYCHIATRY 1570, 1570–71 (1990); Laszlo A. Papp & Jack M. Gorman, *Suicidal Preoccupation During Fluoxetine Treatment*, 147 AM. J. PSYCHIATRY 1380, 1380 (1990); Anthony J. Rothschild & Carol A. Locke, *Reexposure to Fluoxetine After Serious Suicide Attempts by Three Patients: The Role of Akathisia*, 52 J. CLINICAL PSYCHIATRY 491, 491–93 (1991); Gary D. Tollefson, *Fluoxetine and Suicidal Ideation*, 147 AM. J. PSYCHIATRY 1691 (1990).

reports seemed to be sparse compared to the number of patients who had been prescribed an SSRI.<sup>67</sup> In part due to the paucity of reports of suicidal ideation compared to the number of patients taking SSRIs, but also because of confounding factors such as the association of suicidal ideation with depression and concomitant use of other medications in the affected patients, a link between SSRIs and suicidal ideation could not be established without controlled prospective studies.<sup>68</sup> Until 1997, the FDA maintained that there was no credible link between SSRIs and suicidal ideation, as a result of continued monitoring of adverse drug reactions to SSRIs.<sup>69</sup>

Although SSRIs were not initially approved for use in the pediatric population, physicians prescribed SSRIs for children.<sup>70</sup> It was not until there were indications that children and adolescents were vulnerable to suicidal ideation while taking SSRIs that the FDA convened a group of experts to perform a meta-analysis of

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<sup>67</sup> See, e.g., Rothschild & Locke, *supra* note 66, at 493 (reporting on suicide ideation in 3 patients, of approximately 1500 treated). For comparison, suicide ideation appears in the population of primary care patients at a prevalence of one to ten percent. See H.C. Schulberg et al., *Preventing Suicide in Primary Care Patients: The Primary Care Physician's Role*, 26 GEN. HOSP. PSYCHIATRY 337 (2004).

<sup>68</sup> See S.R. Ahmad, *USA: Fluoxetine "Not Linked to Suicide"*, 338 LANCET 875, 875–76 (1991); see also Tollefson, *supra* note 66, at 1692.

<sup>69</sup> See *Motus v. Pfizer*, 127 F. Supp. 2d 1085, 1090 (C.D. Cal. 2000) (discussing FDA's failure to find causal link between Prozac and suicidal ideation). Meta-analysis of available data failed to demonstrate a link between SSRI prescription and suicidal ideation. Marie-Therese Walsh & Timothy G. Dinan, *Selective Serotonin Reuptake Inhibitors and Violence: a Review of the Available Evidence*, 104 ACTA PSYCHIATRICA SCANDINAVICA 84, 88 (2001).

<sup>70</sup> See Rushton et al., *Pediatrician and Family Physician Prescription of Selective Serotonin Reuptake Inhibitors*, 105 PEDIATRICS e82, e82 (2000); *Miller v. Pfizer*, 196 F. Supp. 2d 1095, 1104 (2002) (quoting Thomas Laughren, a senior FDA official, saying "we have no data for [Zoloft] in children . . . and if this drug were to be approved, it is likely that some clinicians will want to use this drug in children," at a Psychopharmacologic Drugs Advisory Committee meeting); see also FDA, *FDA Proposed Medication Guide: About Using Antidepressants in Children or Teenagers*, <http://www.fda.gov/cder/drug/antidepressants/ssrimedicationguide.htm> (updated May 2, 2007). A physician may legally prescribe FDA-approved drugs for non-FDA approved uses if, in his judgment, the prescription is appropriate. This practice is called "off-label" use. See James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71, 71 n.2 (1998).

data from previous studies.<sup>71</sup> Analysis of previous studies suggested a small risk of suicidal ideation in pediatric patients prescribed SSRIs.<sup>72</sup> As a result, the FDA required changes to the labeling of SSRIs to include warning statements “alert[ing] health care providers to an increased risk of suicidality . . . in children and adolescents.”<sup>73</sup>

These examples demonstrate the value of systematic safety research of pharmaceuticals in the post-approval period. Had these drugs been so evaluated, risks would have been revealed sooner. Timely changes to the warning labels or earlier withdrawal of the drug from the market would have minimized harm to patients and saved lives.

The next part of this Note explains why the costs involved in pharmaceutical development, marketing, and ensuring consumer safety are not adequately balanced by incentives to pharmaceutical manufacturers to continue evaluating the safety of their drugs subsequent to FDA approval.

## II. THE CURRENT SYSTEM OF REGULATION DISINCENTIVIZES CONTINUED SAFETY TESTING OF PHARMACEUTICALS

In the pharmaceutical industry, the rewards of market exclusivity guaranteed to a patented drug are dampened by the length of time necessary to develop and evaluate the product for safety and efficacy. A patent is awarded to an inventor of a product or process to reward innovation with market exclusivity.<sup>74</sup> Theoretically, the promise of market exclusivity spurs technological advances.<sup>75</sup> Market exclusivity provides the patentee (or licensee) with a limited time period during which

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<sup>71</sup> See FDA Public Health Advisory, *Suicidality in Children and Adolescents Being Treated with Antidepressant Medications* (Oct. 15, 2004), <http://www.fda.gov/cder/drug/antidepressants/SSRIPHA200410.htm>.

<sup>72</sup> See *id.*

<sup>73</sup> See *id.*; see also FDA, *Antidepressant Use in Children, Adolescents, and Adults* (May 2, 2007), <http://www.fda.gov/cder/drug/antidepressants/default.htm>.

<sup>74</sup> 35 U.S.C. § 154(a)(2) (2006).

<sup>75</sup> Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1597 (2003) (noting that one of the purposes of patent law is to encourage invention).

competition in the market is reduced, thereby increasing the potential profitability of the product.<sup>76</sup> As University of Chicago School of Law Professor Richard Epstein notes, “[t]he medical advances of the past 30 years are not just a matter of dumb luck. They are very heavily dependent on the patent law, pricing freedom, and marketing strategies that have allowed these firms to bring a wide variety of vital products to market.”<sup>77</sup>

Both the expense and duration of testing a drug to obtain FDA approval for marketing impinges on the patent monopoly as the drug cannot be sold prior to approval.<sup>78</sup> Thus, there is little incentive for a pharmaceutical manufacturer to invest time and money into safety testing beyond that required for FDA approval. Yet, the FDA relies on pharmaceutical manufacturers to conduct most of the research on the safety and efficacy of their medications.<sup>79</sup> Once a drug is FDA-approved, there is little economic incentive for a manufacturer to perform ongoing postmarket testing<sup>80</sup> because information revealed by postmarket testing has the potential of restricting the consumer base and does little to protect against products liability suits.

This section discusses three economic reasons underpinning the lack of additional safety testing of pharmaceuticals by their manufacturers: (A) a desire not to impinge upon the exclusive marketing period established by the patent grant, (B) desire not to shrink the market for the drug, and (C) a failure of additional testing to reduce the risk of products liability.

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<sup>76</sup> ROBERT P. MERGES ET AL., *INTELLECTUAL PROPERTY IN THE NEW TECHNOLOGICAL AGE* 127 (4th ed. 2006) (“Patent law provides a market-driven incentive to invest in innovation, by allowing the inventor to appropriate the full economic rewards of her invention.”).

<sup>77</sup> Epstein, *supra* note 4.

<sup>78</sup> See 21 U.S.C. § 355(a) (2006).

<sup>79</sup> See Sage, *supra* note 23, at 1019.

<sup>80</sup> See Jerry Avorn, *Dangerous Deception—Hiding the Evidence of Adverse Drug Effects*, 355 *NEW ENG. J. MED.* 2169, 2170 (2006) (“It is naïve to expect companies to voluntarily fund studies that could sink lucrative products . . .”).

*A. Desire Not to Lose Too Much Exclusivity Period*

The Patent Act<sup>81</sup> grants the patentee the right to exclude others from making, selling, or using the patented product for twenty years from the filing date.<sup>82</sup> This exclusivity period provides economic reward for innovation<sup>83</sup> by eliminating much of the competition for a limited time period.<sup>84</sup> A patent does not grant the right to market the patented product;<sup>85</sup> pharmaceuticals require FDA approval prior to marketing.<sup>86</sup>

Every new prescription drug requires FDA approval prior to entry into interstate commerce.<sup>87</sup> The process between patenting a potential new drug and FDA approval is lengthy and involves considerable expense. The lag time between patenting and FDA approval is typically ten to twelve years.<sup>88</sup> An application to the FDA to market a new drug must follow “adequate and well-controlled” studies and provide “substantial evidence” of safety and efficacy of the new drug.<sup>89</sup> In addition to laboratory research, as many as sixty separate human trials may be required prior to FDA approval.<sup>90</sup> This process erodes the patent term, leaving the

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<sup>81</sup> 35 U.S.C. §§ 1–376 (2006).

<sup>82</sup> *Id.* § 154(a)(2).

<sup>83</sup> The impact of a shortened exclusivity period on pharmaceutical drug innovation is discussed elsewhere and not the subject of this note. *See, e.g.*, James J. Wheaton, *Generic Competition and Pharmaceutical Innovation: The Drug Price Competition and Patent Term Restoration Act of 1984*, 35 CATH. U. L. REV. 433, 449–50 (1986).

<sup>84</sup> *See* MERGES ET AL., *supra* note 76, at 126–27.

<sup>85</sup> *See* Herman v. Youngstown Car Mfg. Co., 191 F. 579, 584–85 (6th Cir. 1911) (“A patent is not the grant of a right to make or use or sell. It does not, directly or indirectly, imply any such right. It grants only the right to exclude others.”) Marketing of a patented product could be blocked by a prior patent. *See* Amgen, Inc. v. Hoechst Marion Roussel, Inc., 339 F. Supp. 2d 202, 288 n.104 (D. Mass. 2004). A “blocking patent situation” arises when an improvement is patented such that the original patent owner can prevent the owner of the improvement patent from using the improved product. *See id.*

<sup>86</sup> *See* 21 U.S.C. § 355(a) (2006).

<sup>87</sup> *See id.*

<sup>88</sup> DENNIS S. FERNANDEZ & JAMES T. HUIE, STRATEGIC BALANCING OF PATENT AND FDA APPROVAL PROCESSES TO MAXIMIZE MARKET EXCLUSIVITY 5, <http://www.iploft.com/PTO-FDA.pdf>.

<sup>89</sup> *See* 21 U.S.C. § 355(d); *see also* Weinberger v. Hynson, Westcott & Dunning, 412 U.S. 609, 617–18 (1973) (interpreting “adequate safety and efficacy testing” and affirming the authority of the FDA to determine whether a drug has met the appropriate standards for approval).

<sup>90</sup> *See* Epstein, *supra* note 4.

pharmaceutical manufacturer with a shorter period of market exclusivity.

In addition, the cost of developing, patenting, and obtaining government approval for a new drug can be staggering. Estimates of the cost of taking a drug from discovery to market range from \$500 million to over \$2 billion.<sup>91</sup> The cost of drug development is correlated with the duration of the FDA approval process. That is, when fewer human studies or human studies of shorter duration are required for FDA approval of a drug, the cost of development is lower.<sup>92</sup> Of course, a shorter FDA approval process leaves more time of market exclusivity associated with the patent term as well.

The effect of the high cost of drug development is exacerbated by the low rate of success. As few as one in ten thousand potential drugs may reach the market.<sup>93</sup> Approximately ten percent of drugs FDA-approved for testing in humans are approved for marketing.<sup>94</sup> Thus, a tiny fraction of drugs brought through the process of discovery, patenting, and research and development make it through FDA approval to marketing.

Following patent expiration, the profits generated from market exclusivity associated with a new drug are severely diminished by competition from generic products.<sup>95</sup> Because profitability of a drug is greatest during the exclusivity period, there is strong

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<sup>91</sup> See Christopher P. Adams & Van V. Brantner, *Estimating the Cost of New Drug Development: Is It Really \$802 Million?*, 25 HEALTH AFF. 420, 427 (2006) (estimating the average cost of drug development to be between \$839 and \$868 million, but varies from \$479 million to \$2.119 billion); J.A. DiMasi, R.W. Hansen & H.G. Grabowski, *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151 (2003) (estimating the average cost of developing a drug at \$802 million); Friedman, *supra* note 33, at 560–62 (2004) (estimating the cost of bringing a drug to market at \$900 million); David Noonan, *Why Drugs Cost So Much*, NEWSWEEK, Sept. 25, 2000, at 22, 26 (estimating the cost of developing a single new drug at over \$500 million).

<sup>92</sup> See Adams & Brantner, *supra* note 91, at 422 tbl.1.

<sup>93</sup> See Office of Technology Assessment (U.S. Government Printing Office), *The Patent-Term Extension and the Pharmaceutical Industry* 13 (Aug. 1981), available at [http://govinfo.library.unt.edu/ota/Ota\\_5/DATA/1981/8119.pdf](http://govinfo.library.unt.edu/ota/Ota_5/DATA/1981/8119.pdf).

<sup>94</sup> See *id.*

<sup>95</sup> See John F. Niblack, *Why are Drug Development Programs Growing in Size and Cost? A View From the Industry*, 52 FOOD & DRUG L.J. 151, 153 (1997) (“Sales of a patented drug product by the original sponsor-innovator . . . can fall by fifty-to-eighty percent in the first year following patent expiration . . .”).

motivation to reduce the portion of the patent term lost to the FDA approval process.<sup>96</sup>

Recognizing the tension between safety testing and patent reward for innovation in the pharmaceutical industry,<sup>97</sup> in 1984 Congress passed the Hatch-Waxman Act,<sup>98</sup> which includes a provision for extending market exclusivity.<sup>99</sup> The Hatch-Waxman Act allows the FDA to extend the term of one patent for a new drug following approval of a New Drug Application (“NDA”) for that drug to compensate for a portion of the time a drug is being studied and reviewed for FDA approval, up to five years.<sup>100</sup> Partially as a result of this provision, the effective patent monopoly of a pharmaceutical has increased from an average of 8.1 years in 1980 to fourteen years in 2000.<sup>101</sup> Still, there is a lag of about eleven years between patent award and FDA approval for marketing for the typical pharmaceutical.<sup>102</sup> During this time, the patent has been disclosed and there is ample opportunity for competitors to develop non-infringing competing products.<sup>103</sup> Loss of market exclusivity time, coupled with the potential for competing products to emerge, prompts pharmaceutical manufacturers to minimize the duration of pre-approval testing.

During the time period prior to FDA approval, the drug is not profitable for the manufacturer because it is not being sold. In addition, considerable funds are being expended for safety and efficacy testing.<sup>104</sup> Moreover, the manufacturer is risking the

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<sup>96</sup> See FERNANDEZ & HUIE, *supra* note 88, at 6 (describing methods drug companies use to reduce the portion of the patent term lost to the FDA approval process).

<sup>97</sup> See *supra* note 92 and accompanying text.

<sup>98</sup> Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. § 355 and 35 U.S.C. §§ 156 and 271(e) (2006)).

<sup>99</sup> See 35 U.S.C. § 156.

<sup>100</sup> See *id.*

<sup>101</sup> See PUBLIC CITIZEN CONGRESS WATCH, RX R&D MYTHS: THE CASE AGAINST THE DRUG INDUSTRY’S R&D “SCARE CARD” 2 (2001), available at <http://www.citizen.org/documents/ACFDC.PDF>.

<sup>102</sup> See FERNANDEZ & HUIE, *supra* note 88, at 1.

<sup>103</sup> Once a patent has been issued, “[t]he specification, drawings and all papers relating to the file . . . are open to inspection by the public.” PTO Records and Files of the Patent and Trademark Office Rule, 37 C.F.R. § 1.11(a) (2008). This can alert competitors to a new market or otherwise spur competitors to develop non-infringing competing products.

<sup>104</sup> See *supra* note 91 and accompanying text.

possibilities that the drug will prove insufficiently safe or effective to obtain FDA approval and that a competing drug will come to the market during this time. Further, the period of exclusivity is the most profitable period for a pharmaceutical.<sup>105</sup> For these reasons, a pharmaceutical manufacturer has considerable economic motivation to minimize the time of pre-approval safety and efficacy research. In fact, pharmaceutical manufacturers have supported legislation to charge themselves user fees to supplement resources to the FDA in order to expedite approval of new drugs.<sup>106</sup> These economic factors disincentivize pharmaceutical companies from performing studies, beyond those required for FDA approval, if those studies would further delay introduction of the drug to the market.

Once a drug is FDA-approved, the incentive to invest additional time and financial resources in ongoing safety testing is further diminished. Continued safety testing may provide little economic reward. As explained in section B, pharmaceutical manufacturers may be reluctant to perform additional studies that may reveal risks that would shrink their potential market and, thereby, further reduce the profitability of such drugs.

*B. Desire Not to Shrink Market as Result of Narrowing Consumer Base*

When pharmaceutical manufacturers perform additional research into the safety of their products, they risk revealing information that may have the effect of narrowing their consumer base. Risks associated with a drug may have a general negative effect on the desire of patients to use that drug, even for those people not at risk or for whom the drug confers a significant benefit. For example, Tysabri (natalizumab), a drug used to mitigate the symptoms of multiple sclerosis, was voluntarily

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<sup>105</sup> See Epstein, *supra* note 4.

<sup>106</sup> See Margaret Gilhooley, *Addressing Potential Drug Risks: The Limits of Testing, Risk Signals, Preemption, and the Drug Reform Legislation*, 59 S.C. L. REV. 347, 351 (2008). Many detractors of the Prescription Drug User Fee Act suggest that it causes the FDA to be accountable to the pharmaceutical industry. Prescription Drug User Fee Act of 1992, Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.); see also Avorn, *supra* note 45, at 1697.

withdrawn from the market in 2005, after several incidences of progressive multifocal leukoencephalopathy.<sup>107</sup> After reintroduction of the drug onto the market in 2006, a survey of multiple sclerosis patients indicated that more than half of those using Tysabri would likely continue to take the drug if it were shown to have a fatality risk of one in one-thousand; over fifteen percent would likely continue to take the drug with a fatality risk of one in one-hundred.<sup>108</sup> Although the actual risk of fatality may be less than one in one-thousand, and the drug significantly reduces multiple sclerosis symptoms, less than twenty-five percent of patients who used Tysabri before its withdrawal from the market resumed taking it after the drug was reintroduced.<sup>109</sup> In this case, the news of a small (although serious) risk resulted in a seventy-five percent reduction in the use of a beneficial drug.

Such risks may also negatively affect physicians' prescribing behavior.<sup>110</sup> This would be especially true if there were similar alternative drugs available. For example, Amgen lost thirty-two percent of its share of the anemia drug market after its drug Aranesp was associated with a risk of potentially fatal cardiovascular events when administered at high doses, suggesting physicians opted to prescribe alternative anemia drugs.<sup>111</sup> A subsequent meta-analysis of a number of studies shows that members of this class of drugs, which includes Johnson & Johnson's Procrit, increase the incidence of blood clots in cancer patients being treated for anemia resulting from chemotherapy.<sup>112</sup> Though all anemia treatments showed a drop in sales, the decline

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<sup>107</sup> Adelman et al., *supra* note 38.

<sup>108</sup> See John E. Calfee, *A Representative Survey of M.S. Patients on Attitudes Toward the Benefits and Risks of Drug Therapy*, 2006 AEI-BROOKINGS JOINT CENTER FOR REG. STUD. 10, available at [http://www.issuelab.org/click/download2/representative\\_survey\\_of\\_ms\\_patients\\_on\\_attitudes\\_toward\\_the\\_benefits\\_and\\_risks\\_of\\_drug\\_therapy/ms\\_patient\\_attitudes.pdf](http://www.issuelab.org/click/download2/representative_survey_of_ms_patients_on_attitudes_toward_the_benefits_and_risks_of_drug_therapy/ms_patient_attitudes.pdf).

<sup>109</sup> See Toni Clarke, *Patients, Doctors Still Leery of Biogen's MS Drug*, REUTERS, Oct. 23, 2006, available at <http://www.reuters.com/article/companyNewsAndPR/idUSN2338680720061023>.

<sup>110</sup> See, e.g., *id.*

<sup>111</sup> See Reuters, *Anemia Drugs May Raise Risk of Death*, BOSTON.COM, Feb. 27, 2008, [http://www.boston.com/business/healthcare/articles/2008/02/27/anemia\\_drugs\\_may\\_raise\\_risk\\_of\\_death/](http://www.boston.com/business/healthcare/articles/2008/02/27/anemia_drugs_may_raise_risk_of_death/).

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

in sales for Aranesp in 2007 was more than two-fold that of the other marketed anemia drugs.<sup>113</sup>

Similarly, the competitive battle between the cox-2 inhibitors, Vioxx and Celebrex, may have contributed to Merck's reluctance to perform the studies to address the potential cardiovascular risks of Vioxx.<sup>114</sup> Although both drugs are in the same class of cox-2 inhibitors and presumably have similar cardiovascular risks,<sup>115</sup> a demonstration of cardiovascular risk associated with Vioxx, but not Celebrex, might have been expected to result in a reduction of the market share for Vioxx.

The potential economic impact of safety studies revealing a risk that would reduce the consumer base serves as an economic disincentive for performing such studies. If the direct expenses and the expense of the effects of additional safety testing were counter-balanced by a reduction in expenses associated with defending products liability suits, such testing might prove economically advantageous. However, as discussed in the next section, the cost of products liability risk may not be reduced by additional safety testing.

*C. Expense of Additional Testing Not Balanced by Cost of Products Liability Risk*

Of course, the safety and efficacy testing required for FDA approval is necessary to ensure consumer safety.<sup>116</sup> However, FDA approval does not ensure the safety of the drug.<sup>117</sup> Continuing use of a drug amongst a heterogeneous population can

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<sup>113</sup> *Id.*

<sup>114</sup> See Margaret Gilhooley, *Vioxx's History and the Need for Better Procedures and Better Testing*, 37 SETON HALL L. REV. 941, 942 (2007). Cardiovascular risks of Vioxx were revealed by studies to demonstrate increased gastrointestinal safety of Vioxx compared to less specific pain relievers and studies for additional uses of the drug. *See id.* at 948. Similar studies were never performed on Celebrex. *See id.* at 945.

<sup>115</sup> See Barry Meier et al., *Medicine Fueled by Marketing Intensified Trouble for Pain Pills*, N.Y. TIMES, Dec. 19, 2004, at A2; Memorandum from John K. Jenkins, M.D. & Paul J. Seligman, M.D., M.P.H. through Steen Galson, M.D., M.P.H. 10 (Apr. 6, 2005), <http://www.fda.gov/cder/drug/infopage/COX2/NSAIDdecisionMemo.pdf> (finding Celebrex and Vioxx are "associated with an increased risk of serious CV events").

<sup>116</sup> See Meadows, *supra* note 15.

<sup>117</sup> See *supra* notes 17–24 and accompanying text.

reveal risks that were not made apparent by earlier human studies.<sup>118</sup> Moreover, the nature of pharmaceuticals is such that a pharmaceutical product can never be “safe” by ordinary standards of product liability.<sup>119</sup> Pharmaceuticals work by interacting with the human body. As a result of variation within the human population, each individual is unique such that a “safe” pharmaceutical may cause undesirable effects in individuals with certain common characteristics<sup>120</sup> as well as undesirable idiosyncratic effects in unique individuals.<sup>121</sup>

Many pharmaceutical products liability cases are based on information that becomes apparent subsequent to initial FDA approval for marketing.<sup>122</sup> Theoretically, the threat of products liability is an attempt to correct for imperfect information.<sup>123</sup> By “promoting information development,” the threat of products liability increases the safety of the product.<sup>124</sup> In other words, the potential for liability for foreseeable risks considering the state of the art at the time of sale motivates pharmaceutical companies to identify risks, via continuing study, and warn of those risks.<sup>125</sup>

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<sup>118</sup> See Woodcock, *supra* note 18; Struve *supra* note 18, at 597–99; see also Sage, *supra* note 23.

<sup>119</sup> See RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY § 2 (1998) (“The issue of foreseeability of risk of harm is more complex in the case of products such as prescription drugs . . .”).

<sup>120</sup> See Funmilayo O. Ajayi et al., *Adverse Drug Reactions: A Review of Relevant Factors*, 40 J. CLINICAL PHARMACOLOGY 1093, 1094 (2000) (explaining that adverse effects of drugs in certain segments of the population are not revealed prior to marketing because pre-approval clinical trials often fail to account for differences among patient groups in terms of age, gender, and other factors which may be common to specific groups).

<sup>121</sup> See *id.* at 1095 (“[G]enetic variability . . . may explain unexpected toxicity demonstrated in some individuals after administration of a usual therapeutic dose [of a drug].”); Sage, *supra* note 23.

<sup>122</sup> See Sage, *supra* note 23, at 1015–16 (discussing the lack of availability of appropriate information when drugs come on the market, as well as other factors, contributing to the incidence of adverse events resulting in products liability cases).

<sup>123</sup> See *id.* at 1015.

<sup>124</sup> See *id.* at 1016.

<sup>125</sup> See, e.g., *Basko v. Sterling Drug, Inc.*, 416 F.2d 417, 426 (2d Cir. 1969) (indicating “there is no duty to warn of unknown or unforeseeable risks”); *Feldman v. Lederle Labs.*, 479 A.2d 374 (N.J. 1984) (limiting liability to risks that were “reasonably knowable”). For a discussion of the behavioral effects of products liability, see Steven Shavell, *Liability for Harm Versus Regulation of Safety*, 13 J. LEGAL STUD. 357 (1984).

Although continued use of a pharmaceutical product over time in a large heterogeneous population may reveal adverse effects that were not apparent at the time of FDA approval, without continued rigorous study it is difficult to evaluate the accumulated data.<sup>126</sup> The result is disagreement as to the significance of the adverse events. At one extreme, the adverse events reveal a risk of drug use that the manufacturer fails to include in the product labeling.<sup>127</sup> Alternatively, the adverse events may be idiosyncratic<sup>128</sup> or may result from consumer misuse.<sup>129</sup> However, there may be insufficient information to determine whether there is a risk.<sup>130</sup> These alternatives are resolvable by continuing post-approval safety evaluation of the drug.

Nonetheless, products liability suits may be brought despite clear evaluation and ongoing postmarketing regulatory approval by the FDA and compliance by the pharmaceutical manufacturer. The paradigmatic example is that of Bendectin.

Bendectin was an anti-nausea drug prescribed to pregnant women.<sup>131</sup> Plaintiffs sued the manufacturer, Merrell Dow Pharmaceuticals, alleging that Bendectin caused birth defects,<sup>132</sup> even though physicians, scientists and the FDA claimed otherwise.<sup>133</sup> After fifteen years, over \$100 million in litigation expenses, and losing about forty percent of the cases against it, Merrell Dow Pharmaceuticals removed Bendectin from the

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<sup>126</sup> See Gardiner Harris, *F.D.A. to Expand Scrutiny of Risks from Drugs After They're Approved for Sale*, N.Y. TIMES, May 23, 2008, at A17.

<sup>127</sup> See *supra* text accompanying note 19.

<sup>128</sup> That is, the reaction to the drug may be due to an individual characteristic of the user that fails to indicate a subgroup of individuals sensitive to the drug. See *supra* note 121 and accompanying text.

<sup>129</sup> Consumer misuse may include, for example, misprescribing by the physician, error in dispensing by the pharmacy, and/or misdosing by the physician and/or patient. See Otero et al., *supra* note 25.

<sup>130</sup> See Sage, *supra* note 23, at 1015.

<sup>131</sup> See Joseph Sanders, *From Science to Evidence: The Testimony on Causation in the Bendectin Cases*, 46 STAN. L. REV. 1, 2 (1993).

<sup>132</sup> See *id.* at 4.

<sup>133</sup> See Michael D. Green, *Statutory Compliance and Tort Liability: Examining the Strongest Case*, 30 U. MICH. J.L. REFORM 461, 477 (1997); Lars Noah, *Triage in the Nation's Medicine Cabinet: The Puzzling Scarcity of Vaccines and Other Drugs*, 54 S.C. L. REV. 741, 760 (2003).

market.<sup>134</sup> The Bendectin story demonstrates how, even in the absence of data demonstrating an unsafe product, pharmaceutical manufacturers are not shielded from products liability or products liability litigation. Such suits disincentivize pharmaceutical manufacturers from postmarket safety testing because evidence of safety has little economic value if it does not reduce the costs of litigation and liability.

In addition, compliance with FDA recommendations does not protect a pharmaceutical manufacturer from products liability. Several state courts apply strict liability standards for failure to warn, even when the pharmaceutical manufacturer has no knowledge of risk<sup>135</sup> and other states apply strict liability standards when the manufacturer knew or should have known of the risk.<sup>136</sup> The result is that pharmaceutical manufacturers bear high costs of product liability even when some risks are unknown or known and not adequately included in warnings approved by the FDA.

Under the current regulatory system, the benefit of continued testing is increased safety to the consumer due to better product labeling. One might expect a safer product to benefit the manufacturer with both increased profits due to increased sales or higher pricing and reduced costs due to decreased liability. On the contrary, knowledge of increased risks results in decreased sales of particular drugs, in part because of fears of liability by physicians

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<sup>134</sup> See Green, *supra* note 133; Noah, *supra* note 133.

<sup>135</sup> See, e.g., *Hamilton v. Hardy*, 549 P.2d 1099, 1106–07 (Colo. 1976) (“[A] manufacturer who sells a product in a defective condition unreasonably dangerous to the consumer is subject to liability for physical harm thereby caused, even though the seller has exercised all possible care in the preparation and sale of the product.”); see also *Sharkey v. Sterling Drug, Inc.*, 600 So.2d 701, 707 (La. App. 1st Cir. 1992) (“A manufacturer’s liability for harm caused by ‘unreasonably dangerous per se’ products may be imposed solely on the basis of the intrinsic characteristics of a product irrespective of the manufacturer’s intent, knowledge or conduct.”).

<sup>136</sup> See, e.g., *Feldman v. Lederle Labs.*, 479 A.2d 374, 392 (1984) (applying strict liability when Lederle knew of the risk of tooth discoloration, but failed to warn on advice of FDA); see also *Carlin v. Superior Court*, 920 P.2d 1347, 1350 (Cal. 1996) (“The California courts, either expressly or by implication, have to date required knowledge, actual or constructive, of potential risk or danger before imposing strict liability for a failure to warn.”).

who opt not to prescribe.<sup>137</sup> In addition, disclosure of additional adverse effects narrows the appropriate market for the drug.<sup>138</sup> Moreover, when pharmaceutical manufacturers reveal additional adverse effects of a drug, the result may be increased costs of defending products liability suits,<sup>139</sup> regardless of the outcome.

Over time, liability risks of marketed drugs increase. The greater the use of the drug, the more likely adverse reactions will be reported,<sup>140</sup> resulting in stricter FDA warnings and/or restriction of marketing. Products liability suits based on actual harm, potential harm, or failure to warn adequately of the drugs' side effects frequently follow. Defending these suits is immensely expensive and the outcomes are unpredictable.<sup>141</sup> Thus, the considerable expense of postmarket study would not likely be balanced by an economic benefit to the manufacturer derived from a reduction in products liability litigation.

The economic effects of the current regulatory and legal system disincentivizes pharmaceutical companies from performing safety testing of their products beyond that required for FDA approval. Since the period of market exclusivity enjoyed by a pharmaceutical is reduced by the length of time necessary to develop and evaluate a product for FDA approval, pharmaceutical manufacturers are motivated to reduce the expense and duration of pre-approval testing. Moreover, the expense of postmarket testing is not balanced by economic reward. To the contrary, information revealed by postmarket testing may reduce the consumer base and fail to reduce the expense of defending against products liability suits. Thus, under the current system, additional safety testing of

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<sup>137</sup> See, e.g., *Anemia Drugs May Raise Risk of Death*, BOSTON GLOBE, Feb. 27, 2008, [http://www.boston.com/business/healthcare/articles/2008/02/27/anemia\\_drugs\\_may\\_raise\\_risk\\_of\\_death/](http://www.boston.com/business/healthcare/articles/2008/02/27/anemia_drugs_may_raise_risk_of_death/) (discussing decrease in sales of Aranesp, in part due to physicians' reluctance to prescribe the drug following a study showing increased risk of blood clots).

<sup>138</sup> See Green, *supra* note 133, at 497 (“[W]idespread use of a newly approved drug may also provide new information that has implications for expanding or narrowing indications for use . . .”).

<sup>139</sup> See *id.* at 468.

<sup>140</sup> See Woodcock, *supra* note 18; Struve *supra* note 18, at 597–99; see also Sage, *supra* note 23.

<sup>141</sup> See, e.g., *supra* notes 131–34 and accompanying text (discussing that, despite a strong consensus that Bendectin was safe, Merrell Dow spent over \$100 million defending product liability suits with unpredictable outcomes).

pharmaceuticals may actually be economically disadvantageous to a manufacturer. A system which provides an economic reward for post-approval safety testing would spur such research. Part III proposes a system to reward post-approval safety testing of marketed pharmaceuticals with an extension of the period of market exclusivity.

### III. SOLUTION: INCENTIVIZE POST-APPROVAL SAFETY TESTING WITH EXTENSION OF MARKET EXCLUSIVITY

Potential for profit controls the incentive to invest money in research and development.<sup>142</sup> Profit is potentially greatest during periods of exclusivity.<sup>143</sup> Extending the period of exclusivity, because it increases profits, will encourage investment in research and development. In particular, it provides economic incentive for pharmaceutical manufacturers to voluntarily continue evaluation of the safety of the drugs they manufacture and market.

#### A. *The Proposal*

This Note proposes an extension of the period of exclusivity for completion of targeted research requested by or approved by the FDA.<sup>144</sup> Concerns about the risks of an FDA-approved drug raised by pre-approval data, reports of adverse drug reactions, or new scientific information could be addressed by carefully planned prospective human studies. Such studies could be initiated by the drug manufacturer in response to an FDA request to perform such studies and approval of the study design by the FDA. Alternatively, a pharmaceutical manufacturer may initiate the

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<sup>142</sup> See Timothy J. McCoy, *Biomedical Process Patents: Should They Be Restricted by Ethical Limitations?*, 13 J. LEGAL MED. 501, 512 (1992) (explaining profitability of an economic monopoly “drives innovation and capital investment in research and development . . .”).

<sup>143</sup> See Epstein, *supra* note 4; FERNANDEZ & HUIE, *supra* note 88, at 1.

<sup>144</sup> Adverse events, internal research or published research may suggest to the manufacturer the desirability of additional safety studies. A manufacturer should be allowed to seek FDA approval to perform and complete such studies in exchange for extension of the exclusivity period as well.

process by requesting approval of a qualifying study design by the FDA. Under this proposal, pharmaceutical manufacturers who complete the FDA approved postmarketing studies and submit their data to the FDA would be rewarded by an extension of the market exclusivity period.<sup>145</sup> The economic incentive of the reward of an extension of the exclusivity period would complement the current punishment structure for failure to perform requested studies, included in the recent Food and Drug Administration Amendments Act of 2007.<sup>146</sup> Thus, in addition to fines for failure to comply with FDA-mandated post-approval studies, pharmaceutical manufacturers would have economic incentives to identify and perform studies, which may or may not originate with the FDA. In that way, this proposal is broader than the current punishment structure because it has the potential to stimulate the performance of a larger set of appropriate studies.

In addition, this Note proposes including a provision permitting FDA approval of third-party safety testing when manufacturers decline to perform FDA-requested studies. Inclusion of a third-party safety testing provision would increase the likelihood of postmarket study. Manufacturers would be more cooperative in performing requested postmarket studies because of the potential of FDA-approved third-party research revealing the necessity for additional warnings of risk without the advantage of the reward of the extension of the exclusivity period. Third-parties could be

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<sup>145</sup> The length of time of the increase in the market exclusivity period is not the subject of this Note. There are valid reasons for both longer and shorter time frames. In addition, whether a manufacturer could receive multiple extensions for multiple studies on the same pharmaceutical would have to be considered because new safety issues may arise for the same drug. Moreover, some consideration is warranted for extending market exclusivity for all pharmaceuticals with the active ingredient tested. This proposal differs from that of Alastair Wood in that the reward would be for performing the study and sharing the data, and not for producing a “preferred and predefined safety outcome.” Alastair J.J. Wood, *A Proposal for Radical Changes in the Drug-Approval Process*, 355 N. ENG. J. MED. 618, 620 (2006). Also, this proposal differs in that the length of the exclusivity period would not be keyed to the financial risk of drug development. *Id.* at 621–22.

<sup>146</sup> Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.).

incentivized to perform requested postmarket studies by provision of funding for such studies.<sup>147</sup>

*B. Extension of Exclusivity is a Successful Incentive*

Implementation of the proposal to stimulate postmarket safety testing of pharmaceuticals by offering a reward of an extension of the exclusive marketing period, described in Part III.A, is likely to have the desired effect. Previous implementation of a similar process addressing safety of pharmaceuticals in the pediatric population serves as a positive example that extension of the exclusive marketing period is adequate incentive to stimulate research.

To stimulate pharmaceutical manufacturers to test drugs for pediatric use, the Food and Drug Administration Modernization Act (“FDAMA”),<sup>148</sup> passed by Congress in 1997, included a provision for extending market exclusivity for manufacturers who evaluated their drug for safety and efficacy in children.<sup>149</sup> The problem addressed by this Act was the prescription of drugs to children despite the lack of adequate dosing, safety and efficacy data for the pediatric population.<sup>150</sup> Because children are

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<sup>147</sup> Like the Best Pharmaceuticals for Children Act, third parties could be attracted to perform the appropriate studies by earmarking NIH funds for such studies and announcing Requests for Applications (“RFAs”). See Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, § 3(3), 115 Stat. 1408 (2002) (codified as amended in 42 U.S.C. § 290b (2006)).

<sup>148</sup> Food and Drug Administration Modernization Act, Pub. L. No. 105-115, 111 Stat. 2296 (2007) (codified at 21 U.S.C. §§ 301–92 (Supp. 1997)).

<sup>149</sup> 21 U.S.C. § 355a(b) (2000). The main provision, of extension of exclusivity as a reward for evaluation in the pediatric population, was renewed with The Best Pharmaceuticals for Children Act (“BPCA”), passed by Congress in 2002. See generally Holly Fernandez Lynch, *Give Them What They Want? The Permissibility of Pediatric Placebo-Controlled Trials Under the Best Pharmaceuticals for Children Act*, 16 ANNALS HEALTH L. 79 (2007).

<sup>150</sup> Over sixty-five percent of drugs prescribed to children are approved for use only in adults. See Lynch, *supra* note 149, at 82; see also Am. Acad. of Pediatrics Committee on Drugs, *Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations*, 95 PEDIATRICS 286, 286 (1995) (noting eighty-one percent of drugs in the 1991 Physicians’ Desk Reference warn that use in children was not determined to be safe or effective or restrict their use to narrow age groups); Rosemary Roberts, *What’s So Special About Children?*, Presented at the American College of Toxicology 22nd Annual Meeting (Nov. 6, 2001), available at <http://www.fda.gov/cder/>

physiologically different from adults, they sometimes respond differently to drugs.<sup>151</sup> Until the FDAMA, pharmaceutical manufacturers had little economic incentive to perform safety and efficacy studies for pediatric prescription of their drugs.<sup>152</sup> Pediatric trials were not required for FDA approval.<sup>153</sup> Manufacturers could avoid liability for adverse reactions in children by not marketing their drugs for pediatric use and including a warning that the drug had not been evaluated for pediatric use in its product labeling, even though off-label use was permitted.<sup>154</sup>

The FDAMA provided economic incentive for a pharmaceutical manufacturer to conduct safety and efficacy testing, in the pediatric population, of an FDA-approved drug by rewarding such studies with a six month extension of market exclusivity for all products with the active ingredient studied.<sup>155</sup> The reward of the extension of exclusivity is granted in exchange for reporting study data and does not depend on the outcome of the study.<sup>156</sup> Under the 2002 revision of the Best Pharmaceuticals for Children Act (“BPCA”),<sup>157</sup> the FDA can approve the establishment of a private foundation, to support third party research on drugs

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pediatric/presentation/tox\_peds\_nov2001/sld005.htm (indicating lack of information for pediatric use for about three-quarters of prescription drugs).

<sup>151</sup> For example, aspirin can cause serious illness in children with chickenpox or influenza; barbiturates are relaxants in adults, but stimulants in children; amphetamines stimulate adults, but relax children. See Rebecca D. Williams, *How to Give Medicine to Children*, 30 FDA CONSUMER 6, 8–9 (Jan.–Feb. 1996).

<sup>152</sup> See Christopher-Paul Milne, *Exploring the Frontiers of Law and Science: FDAMA’s Pediatric Studies Incentive*, 57 FOOD & DRUG L.J. 491, 491–93 (2002).

<sup>153</sup> See Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Proposed Revision of “Pediatric Use” Subsection in the Labeling, 57 Fed. Reg. 47,423 (Oct. 16, 1992) (codified at 21 C.F.R. pt. 201).

<sup>154</sup> See Lauren Hammer Breslow, *The Best Pharmaceuticals for Children Act of 2002: The Rise of the Voluntary Incentive Structure and Congressional Refusal to Require Pediatric Testing*, 40 HARV. J. ON LEGIS. 133, 142 (2003); see also *Miller v. Pfizer*, 196 F. Supp. 2d 1095, 1106 (2002). Pfizer avoided liability for child’s suicide while taking Zolofit, in part, because the drug had not been tested in children and was clearly labeled “[s]afety and effectiveness in children have not been established.” *Id.*

<sup>155</sup> See Milne, *supra* note 152, at 491.

<sup>156</sup> See generally Breslow, *supra* note 154, at 155–56.

<sup>157</sup> Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002) (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.).

that do not undergo manufacturer-performed pediatric testing.<sup>158</sup> This can even be done during the patent term.<sup>159</sup>

As of March 2004, 346 requests to evaluate prescription drugs for pediatric use were received from pharmaceutical manufacturers, 6 months of exclusivity granted for 97 drugs, and new labels approved for 70.<sup>160</sup> These data indicate that pharmaceutical companies are induced to perform safety testing in exchange for a promise of extended exclusivity of marketing, as proposed in Part III.A of this Note. Alternative solutions, discussed in Part III.C of this Note, have proved inadequate to address pharmaceutical safety because they are responsive to harm already caused, do not provide sufficient economic incentive to perform postmarket safety studies, and do not stimulate research focused on specific questions of product safety.

### *C. Alternative Solutions Do Not Work*

#### 1. Products Liability is Insufficient to Ensure Safety

Products liability is invoked as a mechanism to incentivize pharmaceutical companies to perform the safety studies necessary to avoid the expense of liability and litigation.<sup>161</sup> However, the threat of litigation and potential liability has not proven sufficient to stimulate voluntary postmarket studies addressing drug safety because the risk of litigation and liability for failure to warn of adverse responses to a drug does not necessarily correlate to the potential for injury due to drug use.<sup>162</sup> As noted above, the cost of litigation and liability for Bendectin was considerable, despite over

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<sup>158</sup> 42 U.S.C. § 290b (2006).

<sup>159</sup> 21 U.S.C. § 355a(n)(1)(A) (2006).

<sup>160</sup> See Rosemary Roberts, *FDA Perspective on FDAMA: Successes, Failures; Future Directions*, <http://www.fda.gov/cder/pediatric/presentation/FDAMA-FDA%20Persp-Roberts2004/sld008.htm> (last visited Oct. 30, 2008). As of Feb. 19, 2008, 145 drugs have been granted pediatric exclusivity. U.S. Food and Drug Admin., *Drugs to Which FDA has Granted Pediatric Exclusivity for Pediatric Studies under Section 505A of the Federal Food, Drug, and Cosmetic Act*, <http://www.fda.gov/cder/pediatric/exgrant.htm> (last visited Feb. 19, 2008).

<sup>161</sup> See *supra* notes 123–125 and accompanying text.

<sup>162</sup> See *supra* notes 131–134 and accompanying text.

thirty-five scientific studies demonstrating no elevated risk of birth defects with use of the drug.<sup>163</sup>

In addition, products liability cases have resulted in the unavailability of pharmaceuticals that may have beneficial effects which outweigh risks in, at least, a portion of the population.<sup>164</sup> For example, Bendectin, the only anti-nausea drug available for pregnant women in 1983, was voluntarily removed from the market because of the costs associated with products liability litigation.<sup>165</sup> Choices of female contraceptives are limited because of withdrawal of some contraceptive products from the market and disinterest in contraceptive research and development because of liability concerns.<sup>166</sup> A recombinant Lyme disease vaccine was withdrawn from the market because a series of product liability cases resulted in bad publicity, causing a drop in demand even though the adverse events litigated over were never shown to be caused by the vaccine.<sup>167</sup>

An unintended effect of products liability cases is a loss of confidence in the safety of drugs individuals are prescribed. In the wake of products liability cases revealing serious risks of commonly used drugs, approximately twenty percent of adults

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<sup>163</sup> See *Turpin v. Merrell Dow Pharms., Inc.*, 959 F.2d 1349, 1354–56 (6th Cir. 1992) (summarizing the results of six typical clinical studies showing no statistically significant increase in birth defects amongst over 5,000 women prescribed Bendectin during pregnancy compared to those who were not).

<sup>164</sup> The potential for products liability may also discourage new product development, resulting in social harm caused by the absence of product availability. See Sage, *supra* note 23, at 990.

<sup>165</sup> See *Brown v. Superior Court*, 751 P.2d 470, 479 (Cal. 1988).

<sup>166</sup> See David Hubacher, *The Checkered History and Bright Future of Intrauterine Contraception in the United States*, 34 PERSP. ON SEXUAL & REPROD. HEALTH 98, 98 (Mar.–Apr. 2002) (suggesting that limited availability and use of the intrauterine device in the United States is due to withdrawal of products from the market in the 1970s and 1980s, reluctance of companies to develop new devices, as well as other factors not entertained in this paper); Sheldon Segal, *Introduction*, 23 N.Y.U. REV. L. & SOC. CHANGE 329, 330–31 (1997).

<sup>167</sup> See Allison Abbott, *Lyme Disease: Uphill Struggle*, 439 NATURE 524, 524 (2006) (reporting that products liability suits and bad publicity caused GlaxoSmith Kline to pull the vaccine from the market); Emma Hitt, *Poor Sales Trigger Vaccine Withdrawal*, 8 NATURE MED. 311 (2002); see also Editorial, *When a Vaccine is Safe*, 439 NATURE 509 (2006) (reporting that rumors of nonexistent side effects of the vaccine forced it from the market).

regularly taking medication worry about the dangers of the drugs they are taking; thirteen percent stop using drugs prescribed to them; four percent reduce the dosage of drugs they are taking.<sup>168</sup> Consumer choice to stop using or to reduce the dosage of prescription medications can have serious negative consequences to their health.

On the other hand, products liability litigation may encourage the inclusion of unwarranted warnings that go beyond what is required by the FDA.<sup>169</sup> Such suits do not constitute a prospective well-designed study enabling the determination of specific risks that could be adequately warned against in product labeling.<sup>170</sup>

More importantly, the delay in revelation of information between FDA approval and products liability cases results in injury to individuals. For example, an FDA epidemiologic study revealed that in the five years Vioxx was marketed, the use of Vioxx over Celebrex resulted in 27,785 excess acute myocardial infarctions and sudden cardiac deaths.<sup>171</sup>

While products liability suits allow individuals harmed by unsafe drugs to be compensated for their injuries, they do not replace well-designed prospective studies which might have the effect of reducing harm to patients. Rewarding postmarket safety studies of pharmaceuticals with an extension of the exclusive marketing period, as this Note proposes, would incentivize

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<sup>168</sup> See Harris Interactive, *The Public Has Doubts About the Pharmaceutical Industry's Willingness to Publish Safety Information About Their Drugs in a Timely Manner*, HARRIS POLL, at 1 (Jan. 18, 2005), available at [http://www.harrisinteractive.com/news/newsletters/wsjhealthnews/WSJOnline\\_HI\\_Health-CarePoll2005vol4\\_iss01.pdf](http://www.harrisinteractive.com/news/newsletters/wsjhealthnews/WSJOnline_HI_Health-CarePoll2005vol4_iss01.pdf) (online poll of 2,404 US adults conducted in January 2005).

<sup>169</sup> Requirements on Content and Format of Labeling for Human Prescription Drug and Biologic Products, 71 Fed. Reg. 3,921, 3,935 (Jan. 24, 2006); Gilhooley, *supra* note 106, at 353.

<sup>170</sup> See Gilhooley, *supra* note 106, at 353. ("Product liability suits are a less-than-ideal vehicle for determining what type of warning is needed and involve a retrospective determination that the drug sponsor did not do enough.")

<sup>171</sup> Memorandum from David J. Graham, Associate Director of Science, Office of Drug Safety to Paul Seligman, Acting Director, Office of Drug Safety, Risk of Acute Myocardial Infarction and Sudden Cardiac Death in Patients Treated with COX-2 Selective and Non-Selective NSAIDs 9 (Sept. 30, 2004), available at <http://www.fda.gov/CDER/DRUG/infopage/vioxx/vioxxgraham.pdf> (last visited Feb. 11, 2008).

pharmaceutical companies to design studies targeted at elucidating specific risks associated with the drugs studied.

## 2. Fines Become Cost of Doing Business

The FDA has the ability to request post-approval studies of pharmaceuticals.<sup>172</sup> Until recently, however, because the agency had no enforcement power, these studies went largely unperformed.<sup>173</sup> Recent amendment to the Food, Drug and Cosmetics Act allows the FDA to fine manufacturers who fail to perform requested post-approval safety testing.<sup>174</sup> This mechanism of enforcement has not yet been tested. However, the maximum fine of \$10 million<sup>175</sup> is only a small percentage of the average cost of drug development.<sup>176</sup> Manufacturers may risk the possibility of a fine being levied because the expense of a fine may be less than the expense of research and the effect of risks revealed on the marketing of the pharmaceutical. That is, the fine may become the cost of doing business.

## 3. Strengthening Requirements for FDA Approval is Too Costly

An alternative to postmarketing research, is to increase the extent of safety and efficacy studies required for initial FDA approval. Such studies, however, would result in added delay in introducing beneficial drugs to the market.<sup>177</sup> In addition, increasing the scope and number of pre-approval studies would increase the cost of drug development, while the time delay in introduction of the drug to the market would decrease profits. These conditions decrease manufacturers' incentives to develop new drugs.

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<sup>172</sup> See 21 U.S.C. § 355(o)(3)(A) (Supp. 2007); *supra* notes 44–45 and accompanying text.

<sup>173</sup> See Avorn, *supra* note 45, at 1699 and accompanying text.

<sup>174</sup> Food and Drug Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.).

<sup>175</sup> 21 U.S.C. § 333(f)(4)(A)(ii).

<sup>176</sup> The average cost of drug development is about \$800 million. See *supra* note 91 and accompanying text.

<sup>177</sup> Sean M. Basquill, *Prescription Drug Liability and Postmarketing Surveillance: A Modest Proposal*, 25 TEMP. J. SCI. TECH. & ENVTL. L. 69, 76–77 (2006).

As one court recognized, “[p]ublic policy favors the development and marketing of beneficial new drugs, even though some risks . . . might accompany their introduction, because drugs can save lives and reduce pain and suffering.”<sup>178</sup> Increasing the extent of research required for FDA approval may delay access to beneficial drug therapies<sup>179</sup> due to the increased time necessary to perform these additional studies. A cost/benefit analysis of impact of a reduction in drug review time resulting from implementation of the Prescription Drug User Fee Act (“PDUFA”)<sup>180</sup> suggested an overall increase in the health of the population represented by a total increase of 180,000 to 310,000 life-years.<sup>181</sup> These data suggest that a delay in approval time might have a negative impact on the health of the population.

The negative impact of delayed FDA approval may not be sufficiently balanced by increased safety of FDA-approved drugs. Additional pre-approval safety testing may fail to reveal some risks.<sup>182</sup> For many drugs, the potential risks are revealed during the post-approval period.<sup>183</sup> Without the insight of potential risk revealed via post-approval use, targeted studies could not be designed. In addition, whatever studies are implemented in the pre-approval period would not address any risks that remain unanticipated. The incentive to study risks revealed in the post-approval period would not only be lacking, but would be diminished because of the further loss of exclusive marketing time due to the increased pre-approval period. This problem is

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<sup>178</sup> *Brown v. Superior Court*, 751 P.2d 470, 479 (Cal. 1988).

<sup>179</sup> *See* Basquill, *supra* note 177, at 76–77.

<sup>180</sup> Prescription Drug User Fee Act of 1992, Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.) (providing for the FDA to charge a fee to a prescription drug manufacturer for the FDA approval process). The recent fee was increased in order to provide necessary resources to the FDA in order to shorten the approval period. *See* Prescription Drug User Fee Act Meeting Notice, 72 Fed. Reg. 1743, 1746–47 (Jan. 16, 2007), available at <http://www.fda.gov/OHRMS/Dockets/98fr/07-122.htm>.

<sup>181</sup> *See* Tomas J. Philipson, Ernst R. Berndt, Adrian H.B. Gottschalk & Matthew W. Strobeck, *Assessing the Safety and Efficacy of the FDA: The Case of the Prescription Drug User Fee Acts 7* (Nat’l Bureau of Econ. Research, Working Paper No. 11724, 2005), available at <http://www.nber.org/papers/w11724>.

<sup>182</sup> *See* Basquill, *supra* note 177, at 76–77.

<sup>183</sup> *See* Struve, *supra* note 18, at 598–99 and accompanying footnotes.

addressed by the proposal, in Part III.A, to incentivize post-approval safety testing targeted at elucidating potential risks revealed during the postmarket period, without delaying the introduction of pharmaceuticals approved for use.

#### 4. Tax Incentives Are Not Focused on the Problem

While tax incentives have been used to affect behavior in numerous industries,<sup>184</sup> there are a number of disadvantages to utilizing a tax incentive<sup>185</sup> to increase safety testing of pharmaceuticals. First, there is the political concern about giving a tax incentive to an extremely profitable industry. Second, the loss of tax revenue would increase the tax burden (or alternatively reduce services) to the entire populace. Third, there would be no simple mechanism for matching the tax incentive to where the research would have the most beneficial effect. That is, it would be difficult to target the specific pharmaceutical in need of further safety testing in exchange for the tax incentive.

The current Internal Revenue Code<sup>186</sup> allows expenditures on research to be treated as a deduction.<sup>187</sup> A research tax credit provision gives a credit for “qualified research expenses” and “basic research payments” to business entities engaged in research activities.<sup>188</sup> These tax incentives are designed to stimulate general research<sup>189</sup> relevant to the development of new

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<sup>184</sup> See Susan Feigenbaum & Thomas Jenkinson, *Government Incentives for Historic Preservation*, 37 NAT'L TAX J. 113, 117 (1984) (tax incentives have stimulated historic preservation programs). *But see* Salvatore Lazzari, *An Economic Evaluation of Federal Tax Credits for Residential Energy Conservation*, in 7 STUDIES IN TAXATION, PUBLIC FINANCE AND RELATED SUBJECTS—A COMPENDIUM 82, 87–95 (Fund for Public Policy Research 1982) (tax credits have had little to no effect on stimulated residential energy conservation). See generally HOW TAXES AFFECT ECONOMIC BEHAVIOR (Henry J. Aaron & Joseph A. Pechman eds., 1981) (explaining the impact of taxation on allocation of resources in specific areas).

<sup>185</sup> See generally Edward A. Zelinsky, *Efficiency and Income Taxes: The Rehabilitation of Tax Incentives*, 64 TEX. L. REV. 973, 973–74 (1986) (addressing the inefficiency of tax incentives).

<sup>186</sup> Internal Revenue Code, 26 U.S.C. (2006).

<sup>187</sup> *Id.* § 174(a)(1).

<sup>188</sup> Section 41 of the Internal Revenue Code establishes a tax credit for “qualified research expenses” and “basic research payments.” *Id.* § 41(a).

<sup>189</sup> S. REP. NO. 97-144, at 13 (1981), *reprinted in* 1981 U.S.C.C.A.N. 105, 120.

pharmaceuticals and are generally not applicable to research on already existing pharmaceuticals.<sup>190</sup> There is an additional tax credit for qualified clinical testing of drugs to treat specific rare diseases.<sup>191</sup> Thus, these general provisions do not apply to postmarket safety testing.

It would be possible to amend the Internal Revenue Code to include a tax credit for postmarket safety testing of pharmaceuticals. However, such a credit would likely be a general provision, not directed at performing specific studies in response to adverse drug events or scientific evidence suggesting a need to evaluate a specific risk of a specific drug. In addition, an important aspect of the research is that it is well-designed to address the relevant inquiry.<sup>192</sup> To that end, involvement of the FDA in the approval of the study design is vital to the goal of improving the safety of specifically identified pharmaceuticals.<sup>193</sup>

Unlike a tax credit for general postmarketing research, an FDA-administered incentive could be aligned to specific interests. The patent term extension would be applied to the pharmaceutical evaluated. The mechanism of the provision could be structured such that a manufacturer would be required to obtain FDA approval to qualify for the incentive.<sup>194</sup> In addition, the provision could be activated by a request from the FDA. The process would not involve movement of funding from the government to the already profitable pharmaceutical industry. In fact, the PDUFA<sup>195</sup> requires companies using the FDA approval process to pay a user

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<sup>190</sup> See Nina J. Crimm, *A Tax Proposal to Promote Pharmacologic Research, to Encourage Conventional Prescription Drug Innovation and Improvement, and to Reduce Product Liability Claims*, 29 WAKE FOREST L. REV. 1007, 1069–70 (1994). It is conceivable that research into utilizing an already existing pharmaceutical for an entirely new application or delivery system would qualify under the existing Internal Revenue Code. *Id.*

<sup>191</sup> See 26 U.S.C. § 45C.

<sup>192</sup> 21 C.F.R. §314.126 (2008) (laying out the requirements of an adequate and well-controlled study).

<sup>193</sup> See THE FUTURE OF DRUG SAFETY, *supra* note 1, at 1.

<sup>194</sup> Similar to the Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, § 409I(a), 115 Stat. 1408, 1408–1409 (2002) (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.).

<sup>195</sup> Prescription Drug User Fee Act of 1992, Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.).

fee.<sup>196</sup> The current reauthorization of the PDUFA raised the amount of that user fee in order to pay for increased costs associated with more extensive postmarketing surveillance.<sup>197</sup> A tax break to manufacturers implementing postmarketing studies would effectively reduce the funding to the FDA, especially that which is needed to monitor the increased workload due to those studies.

Unlike a tax incentive, a patent term extension would not reduce tax revenues. A reduction in tax revenues may need to be balanced by increasing the tax burden of all taxpayers. On the other hand, the potential increased financial burden on consumers resulting from higher prices of a drug during an extended exclusivity period would be borne by the consumers of the drug who are benefiting from its increased safety. Any financial burden on the pharmaceutical company for performing the necessary research would be offset by the increased revenue during the extended exclusivity period.

The proposal to incentivize postmarket safety evaluation of pharmaceuticals by extension of the exclusivity period, proposed in Part III.A, would have no direct effect on general tax revenues or resources allocated to the FDA. In addition, unlike a tax incentive, which addresses a general industry goal, the proposal herein would enable tying the reward to specific well-designed studies addressing specific safety concerns of identified pharmaceuticals that would be vetted through the FDA for approval prior to initiation.

## CONCLUSION

Recent products liability suits, withdrawal of pharmaceuticals from the market, and changes in product labeling suggests that the

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<sup>196</sup> 21 U.S.C. § 379h (2006).

<sup>197</sup> See Prescription Drug User Fee Act Meeting Notice, 72 Fed. Reg. 1743, 1750 (Jan. 16, 2007), available at <http://www.fda.gov/OHRMS/Dockets/98fr/07-122.htm>. The FDA's 5-year PDUFA plan draft is available at [http://www.fda.gov/cder/pdufa/PDUFA\\_IV\\_5yr\\_plan\\_draft.pdf](http://www.fda.gov/cder/pdufa/PDUFA_IV_5yr_plan_draft.pdf).

current mechanism for safety evaluation of pharmaceuticals is inadequate. Pharmaceutical manufacturers have little incentive to perform postmarket clinical studies to evaluate safety of FDA-approved drugs. The FDA's mechanism to enforce postmarket evaluation is currently inadequate as drug companies are likely to pay penalties in lieu of conducting postmarket research. Products liability, alone, is insufficient to stimulate pharmaceutical manufacturers to avoid litigation by revealing safety indications via postmarket research. In addition, the lack of correlation between risks associated with drug use and potential for expense associated with litigation removes some value from the threat of products liability litigation.

Pharmaceutical manufacturers can be incentivized to perform postmarket safety research by rewarding such research with extension of market exclusivity. This incentive has proven to be an effective stimulus to induce pharmaceutical manufacturers to evaluate FDA-approved drugs for pediatric use. The mechanism proposed herein, modeled on the Best Pharmaceuticals for Children Act, provides an economic incentive for pharmaceutical manufacturers to perform targeted research to evaluate FDA-approved drugs. The research would result in increased information on the risks of use of specific pharmaceuticals which would have a significant impact on the safety of pharmaceutical consumers.