

# FACILITATING INFORMED MEDICAL TREATMENT THROUGH PRODUCTION AND DISCLOSURE OF RESEARCH INTO OFF-LABEL USES OF PHARMACEUTICALS

MITCHELL OATES\*

*Pharmaceutical manufacturers must conduct extensive research to prove the safety and efficacy of a new drug before it can be sold to the public. However, once the Food and Drug Administration (FDA) approves a drug for one use, doctors may prescribe it to patients for any purpose for which they believe it may be beneficial. Because manufacturers are not required to prove the efficacy of a product for these "off-label" uses, research upon which physicians might base treatment decisions involving novel uses of approved drugs is likely to be lacking. In this Note, Mitchell Oates addresses two interrelated problems: a lack of research into off-label uses of pharmaceutical products and a failure, when such research is undertaken in the first place, to ensure that the findings are made public. He argues that there are limited incentives for pharmaceutical manufacturers to conduct research into the efficacy of off-label uses of their approved products. Furthermore, even when a manufacturer does conduct such research, the public benefit that results is uncertain because the manufacturer is under no obligation to publish or otherwise disseminate the data, and it is unlikely to voluntarily release research findings that might be damaging to sales. While manufacturers must submit summaries of post-approval research to the FDA, public access to these data is blocked by various legal provisions that protect against the release of trade secrets and confidential commercial information. Oates argues that the application of such provisions to data pertaining to off-label uses is inappropriate because the release of such data is unlikely to cause competitive harm to the manufacturers whose research is disclosed. In light of the problems identified and the lack of legitimate objections based on competitive harm, manufacturers should be required to conduct research into some off-label uses of their products and to disclose the data in a form useful to practitioners. Oates concludes by outlining a potential solution, modeled after an existing legislative scheme, the Best Pharmaceuticals for Children Act.*

## INTRODUCTION

The Food and Drug Administration's (FDA) approval process generally guarantees that novel pharmaceutical products will not reach the market unless they will provide some benefit to at least some class of patients. However, there is at least one significant gap in the protection provided under the current system. Typically, FDA

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\* Copyright © 2005 by Mitchell Oates. B.S., 1997, University of Michigan; M.S. in Neurosciences, 2001, University of California, San Diego; J.D., 2005, New York University School of Law. I would like to thank Rochelle Dreyfuss, Taja-Nia Henderson, Brianne Lucyk, George Luscombe, Lars Noah, Steve Perry, Hunter Tart, and Diane Zimmerman. Thanks also to my family and friends.

approval is based on the conclusion, supported by data from clinical trials, that a compound is safe and effective in treating a particular condition, sometimes for a limited class of patients.<sup>1</sup> Once a drug receives FDA approval, however, a physician may prescribe it to *any* patient, for the treatment of *any* condition for which the physician believes it might be beneficial. The physician may also vary the dosage or route of administration at his discretion. Because such “off-label” uses of a drug are not examined during the approval process,<sup>2</sup> it is likely, especially when the use is relatively uncommon, that little or no research will have been conducted to investigate the safety or efficacy of the drug for this purpose.

The lack of research into off-label uses of pharmaceuticals frustrates the effective practice of evidence-based medicine (EBM), an approach that emphasizes the use of reliable scientific evidence in making medical treatment decisions.<sup>3</sup> EBM urges physicians to ground their decisions “conscientious[ly], explicit[ly] and judicious[ly]” in sound scientific research, ideally in well-designed, controlled clinical trials.<sup>4</sup> While EBM has its critics, its central rationale—that reliance upon higher-quality forms of evidence is likely to improve treatment outcomes—seems unassailable.<sup>5</sup> When a physician faces a decision whether to prescribe a drug off-label, and the relevant research has never been conducted, he has no choice but to depend upon less reliable information, which may not lead to optimal treatment decisions.<sup>6</sup>

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<sup>1</sup> See *infra* Part I.A.

<sup>2</sup> Unapproved uses are referred to as “off-label” uses because the labeling information that accompanies a pharmaceutical product is only permitted to include information relating to approved uses. See *infra* Part I.B.

<sup>3</sup> See generally Evidence-Based Medicine Working Group, *Evidence-Based Medicine: A New Approach to Teaching the Practice of Medicine*, 268 JAMA 2420 (1992) (describing paradigm shift toward evidence-based medicine (EBM)).

<sup>4</sup> David L. Sackett et al., *Evidence Based Medicine: What It Is and What It Isn't*, 312 BRIT. MED. J. 71, 71 (1996); see also Dan Mayer, *Evidence-Based Medicine*, 36 NEW ENG. L. REV. 601, 602 (2002) (explaining that EBM stresses importance of “interpreting and applying the medical literature in the most accurate way” and increased awareness of value of randomized clinical trials).

<sup>5</sup> See William A. Ghali et al., *Evidence-Based Medicine and the Real World: Understanding the Controversy*, 5 J. EVALUATION CLINICAL PRAC. 133, 133–38 (1999) (discussing controversy surrounding EBM and refuting some arguments frequently offered by critics).

<sup>6</sup> An important motivation for the EBM movement was the perception that doctors too often relied upon unscientific sources of information and rarely questioned treatments inherited from previous generations, even though the efficacy of these treatments often had never been investigated in any systematic way. See Mayer, *supra* note 4, at 605 (contrasting evidence-based and “[e]minence-[b]ased” approaches). Instead, treatments were developed on the basis of some combination of intuition, anecdotal reports, unsystematic clinical observation, and pathophysiologic reasoning (the practice of predicting, without empirical support, the effects of a medical treatment using general principles of physiology

It is estimated that forty to sixty percent of all prescriptions are written for off-label uses.<sup>7</sup> Given the frequency of this practice, it is particularly important to provide some assurance that these treatments are likely to be effective. In order for medicine to function according to the ideals of EBM, based on an up-to-date and reliable scientific foundation, research should not end once a product is granted FDA approval. However, FDA regulations do not currently require such research and, given its cost,<sup>8</sup> it is unlikely to be undertaken by any party but the manufacturer. A manufacturer might voluntarily decide to undertake research into off-label uses of its products, but whether this occurs will depend upon the economic incentives involved, and there is reason to believe that these incentives are less than robust.<sup>9</sup>

Importantly, even when manufacturers are willing to undertake clinical trials investigating unapproved uses, this research is of no benefit to medicine unless the results are disclosed in some form that the medical community is able to evaluate and utilize effectively. However, pharmaceutical manufacturers are obviously not eager to disseminate information that is unfavorable to their products, and other parties face significant obstacles that may prevent access to and dissemination of this information.<sup>10</sup> The overall result is that the findings of these studies may remain undisclosed and unavailable to physicians who will prescribe drugs for the very off-label uses that were under investigation.

This problem would not be solved simply by imposing a disclosure obligation on manufacturers, because such an obligation would likely reduce the already weak incentives to produce this research in the first place. Under the existing system, a manufacturer's choice to invest in research is made in light of the fact that it can avoid the consequences of publishing unfavorable results. If disclosure were mandatory, the possibility that a negative result would reduce profits might lead a manufacturer not to undertake these studies at all.

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and disease processes). See Ghali et al., *supra* note 5, at 134 (describing case in which pathophysiologic reasoning led to different conclusion than that borne out by data as "a situation in which pathophysiologic rationale suggesting benefit (i.e. 'reducing ventricular ectopy must also reduce clinically significant arrhythmias') has been supplanted by . . . evidence . . . from a well-designed clinical study"); Lars Noah, *Medicine's Epistemology: Mapping the Haphazard Diffusion of Knowledge in the Biomedical Community*, 44 ARIZ. L. REV. 373, 378-91 (2002) (discussing various sources of biomedical knowledge).

<sup>7</sup> Kaspar J. Stoffelmayr, Comment, *Products Liability and "Off-Label" Uses of Prescription Drugs*, 63 U. CHI. L. REV. 275, 278 (1996).

<sup>8</sup> See *infra* note 29 and accompanying text.

<sup>9</sup> See *infra* Part II.A.

<sup>10</sup> See *infra* Part II.B.2.

This Note will examine the interrelated problems of the production and subsequent disclosure of results from clinical trials investigating off-label uses of pharmaceuticals. Part I will provide background, discussing issues surrounding pharmaceuticals generally, the FDA new drug approval process, the importance of off-label prescriptions to modern medicine, and some reasons why manufacturers might possess insufficient incentives to conduct research into off-label uses of their products. Part II will describe the important connection between production of research and disclosure of the results, and will discuss some reasons why disclosure is not effectively guaranteed under current conditions. This Part will next examine and ultimately reject claims that a disclosure obligation would cause significant commercial harm to manufacturers, and will consider arguments for placing such an obligation on the manufacturer, rather than on the FDA. Finally, Part III will introduce an outline of a potential solution, modeled after an existing legislative scheme, the Best Pharmaceuticals for Children Act. This solution would require manufacturers to undertake research into the efficacy of certain off-label uses in exchange for compensation, and would include a mandatory obligation to make the results of the research publicly available.

## I

### BACKGROUND: PHARMACEUTICALS AND PHARMACEUTICAL REGULATION

#### A. *Pharmaceuticals and the FDA Approval Process*

While few would debate the importance of drug treatment in the modern practice of medicine and the potential social value of promoting innovation in the pharmaceutical industry, it is also true that pharmaceuticals can pose significant dangers to consumers. Even a drug designed to treat a relatively uncommon condition may be used by hundreds of thousands of consumers,<sup>11</sup> in many cases multiple times per day for an extended, sometimes indefinite, period.<sup>12</sup> There-

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<sup>11</sup> The Orphan Drug Act provides incentives to manufacturers for developing drugs for the treatment of rare conditions, defined in part as those affecting patient populations of 200,000 or fewer. See 21 U.S.C. § 360bb(a)(2) (2000).

<sup>12</sup> Of course, for products used to treat more common conditions, a variety of conditions, or less well-defined conditions, the potentially affected population is much larger. See, e.g., Leticia M. Diaz, *Regulating the Administration of Mood-Altering Drugs to Juveniles: Are We Legally Drugging Our Children?*, 25 SETON HALL LEGIS. J. 83, 86-87 (2001) (discussing overprescription of Ritalin due to inadequate definition of attention deficit/hyperactivity disorder); Heather Stewart, *Cholesterol Buster Raises Safety Concerns*, GUARDIAN (London), Mar. 12, 2004, at 20 (stating that eleven million Americans use statins to reduce cholesterol levels, and that this number would increase threefold if government recommendations for use were followed).

fore, the number of consumers affected by a dangerous drug is potentially very large.

Although other products affect a large number of consumers, pharmaceuticals are particularly problematic because the risks associated with their use are inherent and not easily discoverable. To understand why drugs pose some unique safety concerns requires a brief discussion of the details of pharmacological treatment. In essence, a drug is a vehicle for introducing a biologically active molecule into the body. The drug produces its beneficial effects through interactions between that molecule and one or more particular molecular receptor sites within the body.<sup>13</sup> Most drugs are small molecules with relatively simple chemical structures,<sup>14</sup> lacking absolute specificity for any single molecular target.<sup>15</sup> Such molecules will have some affinity for many receptor sites, and are capable of producing a wide array of biochemical consequences.<sup>16</sup>

It is, for all practical purposes, presently impossible to design a "magic bullet" drug that acts with absolute specificity at the particular site through which it produces its therapeutic effects.<sup>17</sup> Because any drug administered systemically will produce effects throughout the body, even a theoretical drug with exclusive specificity for a single receptor site likely would not produce a single, intended physiological effect. Receptor molecules are not necessarily tissue-specific, and a drug's action in different systems in the body may have very different physiological consequences.<sup>18</sup> Even at its "intended" site of action, a drug may produce multiple effects because the biochemical sequelae of the initial drug-receptor interaction at the cell surface often have

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<sup>13</sup> See ROBERT M. JULIEN, *A PRIMER OF DRUG ACTION: A CONCISE, Nontechnical Guide to the Actions, Uses, and Side Effects of Psychoactive Drugs* 35–36 (7th ed. 1995). The precise details by which this interaction produces physiological change, however, are likely to be unknown. See Edward L. Korwek, *Human Biological Drug Regulation: Past, Present, and Beyond the Year 2000*, 50 *FOOD & DRUG L.J.* 123, 144 (Special 50th Anniversary Issue, 1995).

<sup>14</sup> Bertram G. Katzung, *Introduction to Basic & Clinical Pharmacology* 1, 2–4 (Bertram G. Katzung ed., 7th ed. 1998) (discussing physical properties of drugs).

<sup>15</sup> *THE MERCK MANUAL OF DIAGNOSIS AND THERAPY* 2571 (Mark H. Beers & Robert Berkow eds., 17th ed. 1999) [hereinafter *MERCK MANUAL*].

<sup>16</sup> See *id.*; Henry R. Bourne, *Drug Receptors & Pharmacodynamics*, in *BASIC & CLINICAL PHARMACOLOGY*, *supra* note 14, at 9, 27.

<sup>17</sup> See, e.g., *MERCK MANUAL*, *supra* note 15, at 2571 ("Few if any drugs have absolute specificity . . ."); JOHN MANN, *THE ELUSIVE MAGIC BULLET: THE SEARCH FOR THE PERFECT DRUG* 1–13, 193–97 (1999) (describing historical attempts—and failures—to find "magic bullet" drugs).

<sup>18</sup> For example, opioid drugs such as morphine and heroin produce intended effects of analgesia and euphoria via effects within the brain while simultaneously producing serious gastrointestinal side effects due to action on receptors in the intestine. See JULIEN, *supra* note 13, at 233–48.

implications for cellular processes involved in different functional pathways.<sup>19</sup> Therefore, as a result of the very nature of pharmacological treatment, all drugs have an inherent and unavoidable potential to produce multiple effects, both harmful and beneficial.<sup>20</sup>

Because of our incomplete scientific understanding of the full complexity of human physiology, and of the precise mechanism by which many drugs act,<sup>21</sup> it is difficult to predict with certainty what constellation of effects will result when a drug is administered. Therefore, even for a relatively well-characterized compound, there is no real assurance that a drug will be safe or effective until tested in human clinical trials.

In recognition of the inherent uncertainty associated with the risks and benefits of an untested pharmaceutical product, manufacturers must receive affirmative clearance from the FDA before placing any "new drug" into interstate commerce.<sup>22</sup> FDA approval requires that applicants provide data that constitute "substantial evidence" of a product's safety and effectiveness.<sup>23</sup> This "substantial evi-

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<sup>19</sup> Statins are an example of a class of drugs that can produce two inseparable physiological effects via action at a single initial molecular site. Statins produce their cholesterol-lowering effects through effects on HMG-CoA reductase, an enzyme which catalyzes the production of mevalonate, a necessary precursor in cholesterol biosynthesis. Inhibiting this enzyme reduces levels of mevalonate and decreases cholesterol synthesis. However, mevalonate is also a component in the synthesis of another molecule, Coenzyme Q<sub>10</sub>, or ubiquinone. This enzyme is crucial in the bioenergetic pathway leading to the production of ATP, and interruptions in this pathway in skeletal muscle can lead to cell death and, possibly, rhabdomyolysis, the complication which led to the recall of cerivastatin (Baycol). See, e.g., Emile G. Bliznakov & David J. Wilkins, *Biochemical and Clinical Consequences of Inhibiting Coenzyme Q<sub>10</sub> Biosynthesis by Lipid-Lowering HMG-CoA Reductase Inhibitors (Statins): A Critical Overview*, 15 *ADVANCES IN THERAPY* 218, 219, 224 (1998); Karl Folkers et al., *Lovastatin Decreases Coenzyme Q Levels in Humans*, 87 *PROC. NAT'L ACAD. SCI.* 8931, 8931 (1990); Barry E. Bleske et al., *The Effect of Pravastatin and Atorvastatin on Coenzyme Q<sub>10</sub>*, 142 *AM. HEART J.* E2 (2001), <http://download.journals.elsevierhealth.com/pdfs/journals/0002-8703/PIIS0002870301528100.pdf>.

<sup>20</sup> For example, minoxidil, better known as Rogaine, was originally approved for use in treating heart conditions before its hair restoration properties were known; sildenafil citrate, marketed as Viagra and well-known for its effectiveness in treating erectile dysfunction, was originally developed as a treatment for angina. See Gina Kolata, *Drugs That Deliver More Than Originally Promised*, *N.Y. TIMES*, Apr. 5, 1998, § 4, at 3 (discussing minoxidil and Viagra); *Erectile Dysfunction*, BBC News (UK Ed.), [http://news.bbc.co.uk/1/hi/health/medical\\_notes/104740.stm](http://news.bbc.co.uk/1/hi/health/medical_notes/104740.stm) (last updated Oct. 12, 2004) (discussing Viagra).

<sup>21</sup> See, e.g., Jaime A. Wilsker, *One-Half Phen in the Morning/One Fen Before Dinner: A Proposal for FDA Regulation of Off-Label Uses of Drugs*, 6 *J.L. & POL'Y* 795, 835 (1998) (noting that precise mechanism of action of fenfluramine remains unknown).

<sup>22</sup> See Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 *VA. L. REV.* 1753, 1761–64 (1996) (discussing "new drug" requirement). For a more in-depth review of the development of the Food and Drug Administration (FDA) regulatory system, see generally *id.*

<sup>23</sup> "Substantial evidence" is defined as:

dence" standard has been interpreted by the FDA as requiring at least two "adequate and well-controlled" large-scale clinical trials.<sup>24</sup>

Under the modern regulatory system, before a company may conduct clinical trials in human subjects, the FDA must grant an Investigational New Drug exemption (IND).<sup>25</sup> The IND essentially waives the Food, Drug, and Cosmetic Act's (FD&C Act) general restriction against distributing an unapproved drug in interstate commerce, for the limited purpose of conducting the testing necessary to gain approval.<sup>26</sup> Once an IND has been granted, the company may begin the required clinical testing that will eventually be submitted as part of its New Drug Application (NDA). In order to receive approval of its NDA, the manufacturer must proceed through three stages of clinical testing.<sup>27</sup> The most important component of the NDA approval process is the third phase of testing, which often involves thousands of patients and takes an average of three years to complete.<sup>28</sup> This entire process is lengthy and extremely expensive. To move a single drug through the FDA approval process to market

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evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

21 U.S.C. § 355(d) (2000).

<sup>24</sup> See Merrill, *supra* note 22, at 1771.

<sup>25</sup> To receive an Investigational New Drug exemption (IND), a manufacturer must submit an outline of its research plan and results of required preclinical research, including in vitro and animal studies addressing the toxicity of the drug and, if possible, its potential for therapeutic benefit in humans. See Proposed New Drug, Antibiotic, and Biologic Drug Product Regulations, 48 Fed. Reg. 26,720, 26,723 (proposed June 9, 1983) (codified at 21 C.F.R. pt. 312). See generally Investigational New Drug Application, 21 C.F.R. pt. 312 (2005) (regulating submission and evaluation of INDs).

<sup>26</sup> See 21 U.S.C. § 355(a), (i) (2000); 21 C.F.R. § 312.1(a) (2005).

<sup>27</sup> Phase 1 studies are normally conducted in twenty to eighty healthy human subjects, for the purpose of "determining the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness"; the results are used as a basis for designing appropriate Phase 2 studies. Phase 2 studies are intended to establish a drug's effectiveness for the treatment of a particular condition in controlled clinical trials involving as many as several hundred patients with the condition in question. These studies are also used to identify common short-term side effects and risks. Phase 3 studies include up to several thousand subjects and provide additional information about effectiveness and safety necessary for the FDA's review of the application for approval. See 21 C.F.R. § 312.21 (2005) (outlining three phases of clinical testing); JULIEN, *supra* note 13, at 46-48 (describing FDA approval process).

<sup>28</sup> Charles J. Walsh & Alissa Pyrich, *Rationalizing the Regulation of Prescription Drugs and Medical Devices: Perspectives on Private Certification and Tort Reform*, 48 RUTGERS L. REV. 883, 907 (1996).

has been estimated to require fifteen years and an expense of \$880 million.<sup>29</sup>

Once clinical testing has been completed, a company may submit its NDA, which includes virtually every piece of available information relating to the drug for which approval is sought.<sup>30</sup> Most importantly for the purposes of this Note, the NDA must include all research data, published or unpublished, relating to the compound in question.<sup>31</sup> The sheer volume of information a manufacturer is required to submit is enormous.<sup>32</sup> Though the applicant has already analyzed the data and submitted required summaries of its trials,<sup>33</sup> it must also provide "full reports" from all clinical trials, including essentially all records relating to every participating patient.<sup>34</sup> The FDA then uses these reports to engage in its own independent review of the raw data in order to verify the manufacturer's conclusions.<sup>35</sup>

After the FDA has determined that the clinical data submitted are sufficient to establish a drug's efficacy for the proposed use or uses, the manufacturer must submit labeling information to accompany the product as a package insert.<sup>36</sup> This information is also reprinted in the *Physicians' Desk Reference*,<sup>37</sup> the main source con-

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<sup>29</sup> James O'Reilly & Amy Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 ANNALS HEALTH L. 295, 304 (2003); see also Michael D. Greenberg, *AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process*, 3 N.Y.U. J. LEGIS. & PUB. POL'Y 295, 300 n.24 (2000) (citing estimate of fifteen years and \$500 million); Holly Soehnge, *The Drug Price Competition and Patent Term Restoration Act of 1984: Fine-Tuning the Balance Between the Interests of Pioneer and Generic Drug Manufacturers*, 58 FOOD & DRUG L.J. 51, 52 (2003) (estimating \$250 to \$600 million and nine years).

<sup>30</sup> See 21 U.S.C. § 355(b)(1) (2000) (listing required contents of New Drug Application (NDA)); Walsh & Pyrich, *supra* note 28, at 907-08 ("The NDA . . . contain[s] nearly every piece of information collected about the drug in the course of laboratory and animal testing as well as clinical trials.").

<sup>31</sup> 21 U.S.C. § 355(b)(1) (2000).

<sup>32</sup> The submission of the NDA, before the advent of electronic submission, consisted of the delivery of literally "truckloads" of documents to the FDA. 1 JAMES T. O'REILLY, FOOD AND DRUG ADMINISTRATION § 13:11, at 13-62 (2d ed. 1995). The NDA submitted in support of Prozac is reported to have been one million pages in length. Michael D. Green, *Safety as an Element of Pharmaceutical Quality: The Respective Roles of Regulation and Tort Law*, 42 ST. LOUIS U. L.J. 163, 172 (1998). Even a more typical NDA will often comprise over one hundred thousand pages. See *id.*

<sup>33</sup> 21 C.F.R. § 314.50(c)(2)(viii) (2004).

<sup>34</sup> 21 U.S.C. § 355(b)(1) (2000); see also 21 C.F.R. § 314.50(f) (2004).

<sup>35</sup> See Merrill, *supra* note 22, at 1784, 1849, 1851-52 (describing and criticizing FDA's "full reports" requirement).

<sup>36</sup> See Steven R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 186-87 (1999).

<sup>37</sup> See Jacob B. Nist, *Liability for Overprescription of Controlled Substances: Can It Be Justified in Light of the Current Practice of Undertreating Pain?*, 23 J. LEGAL MED. 85, 89 (2002).



sulted by physicians when prescribing medications.<sup>38</sup> The product labeling must contain "a summary of the essential scientific information needed for the safe and effective use of the drug."<sup>39</sup> Furthermore, "[n]o implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or . . . effectiveness."<sup>40</sup> These requirements ensure that the instructions and information provided to prescribers will correspond only to those uses addressed by the clinical trials that supported the NDA.<sup>41</sup>

### B. Off-Label Uses

In order to minimize the time and money spent in the already lengthy new drug approval process, a drug maker will typically seek initial approval for a small number of uses.<sup>42</sup> Once a product's NDA has been reviewed and approved, however, it may be prescribed to any patient for any condition for which a doctor believes it will be beneficial. In the words of the FDA: "Once the new drug is in a local pharmacy . . . the physician may, as part of the practice of medicine, . . . vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration."<sup>43</sup> Consistent with Congressional intent in enacting the FD&C Act, the FDA has made clear that it does not regulate the practice of medicine.<sup>44</sup>

While the FDA's policy towards unapproved uses might seem puzzling in light of the considerable barriers involved in gaining approval for a product's initial use, off-label use is not necessarily a practice that should be curtailed.<sup>45</sup> Indeed, many believe a hands-off

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<sup>38</sup> See *id.* at 89–90 (stating that nine out of ten physicians use *Physicians' Desk Reference* as their primary reference and ninety-seven percent consult it for unfamiliar drugs).

<sup>39</sup> 21 C.F.R. § 201.56(a) (2004). The product labeling must specifically include sections relating to indications and usage, contraindications, warnings, adverse events, dosage and administration, and other information relevant to the use of the product. 21 C.F.R. §§ 201.56(d)(1), 201.57 (2004).

<sup>40</sup> 21 C.F.R. § 201.56(c) (2004).

<sup>41</sup> See 21 U.S.C. § 355(d) (2000) (requiring substantial evidence of efficacy for uses described in labeling for approval).

<sup>42</sup> See Elizabeth A. Weeks, *Is It Worth the Trouble? The New Policy on Dissemination of Information on Off-Label Drug Use Under the Food and Drug Administration Modernization Act of 1997*, 54 *FOOD & DRUG L.J.* 645, 663 (1999) ("[M]anufacturers usually seek an NDA for a minimal number of indications.").

<sup>43</sup> Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16,503, 16,503 (proposed Aug. 15, 1972) (final rule codified at 21 C.F.R. pt. 130).

<sup>44</sup> See *id.*

<sup>45</sup> Even if government regulation of physicians' prescribing practices were considered desirable, it is questionable whether the FDA has statutory authority to do so, and an attempt to assert such authority is unlikely. See William L. Christopher, *Off-Label Drug*

approach provides a desirable level of freedom, allowing practitioners to pursue innovative treatment strategies, and facilitating the discovery of new uses.<sup>46</sup>

In addition, given the frequency with which physicians resort to off-label prescription, limitations on this treatment option would drastically disrupt medical practice. As noted previously, off-label uses of pharmaceuticals are extremely common in modern medicine, and are particularly important to pediatric medicine and the treatment of cancer, AIDS, and rare diseases.<sup>47</sup> Some have commented that refusal to prescribe a drug for an off-label use would, in many cases, constitute medical malpractice.<sup>48</sup>

Even if off-label prescription is a beneficial practice and should not be prohibited altogether, it will be most beneficial to patients if it is guided by evidence of efficacy based on formal clinical trials. The emergence of an off-label use in the post-approval period merely provides preliminary evidence that a treatment appears promising. Once such a treatment has been identified, research should be conducted to verify that the drug is effective for this purpose. Just as the FDA does not approve new drugs based only on preliminary evidence of efficacy, neither should the unsystematic observations of practicing physicians mark the end of the inquiry into the efficacy of off-label uses of approved drugs. Once a novel and potentially effective use for a drug has been identified, follow-up research is particularly important in order to provide the foundation for evidence-based practice.<sup>49</sup> While some safeguards exist to minimize concerns about adverse events associated with off-label use,<sup>50</sup> the actual *effectiveness* of a drug used

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*Prescription: Filling the Regulatory Vacuum*, 48 FOOD & DRUG L.J. 247, 250–54 (1993) (discussing possibility of FDA regulation of off-label prescription and concluding that FDA is unlikely to proceed in this direction). *But see* Sydney A. Shapiro, *Limiting Physician Freedom to Prescribe a Drug for Any Purpose: The Need for FDA Regulation*, 73 NW. U. L. REV. 801, 801–02 (1978) (advocating more active role for FDA in regulation of physicians' prescribing activities).

<sup>46</sup> See, e.g., Christopher, *supra* note 45, at 249 (noting reports of “serendipitous drug discovery” as result of off-label use); Lars Noah, *Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy*, 28 AM. J.L. & MED. 361, 362 (2002) (discussing ongoing innovation in medical treatment that continues after approval has been granted and noting that “[p]hysicians try things out on their patients all of the time”).

<sup>47</sup> See O'Reilly & Dalal, *supra* note 29, at 298.

<sup>48</sup> See Stoffelmayr, *supra* note 7, at 278–79.

<sup>49</sup> See *supra* notes 1–8 and accompanying text.

<sup>50</sup> FDA regulations require that pharmaceutical manufacturers inform the FDA of any adverse events associated with the use of an approved drug of which the manufacturer becomes aware, and physicians may also make reports directly to the FDA through the Medwatch program. See Barbara A. Noah, *Adverse Drug Reactions: Harnessing Experimental Data to Promote Patient Welfare*, 49 CATH. U. L. REV. 449, 466–81 (2000) (describing

off-label is unlikely to be revealed by any post-approval surveillance mechanism currently in place.<sup>51</sup>

Without scientific data on which to base their decisions regarding off-label prescription, physicians essentially revert back to the practice of medicine as it existed before the introduction of the FDA's premarket approval requirement,<sup>52</sup> when the clinical utility of a drug

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existing programs for adverse event monitoring in post-approval period). Of course, recent experience has made clear that this system is by no means infallible. See Press Release, Ctr. for Drug Evaluation & Research, FDA, FDA Announces Withdrawal of Fenfluramine and Dexfenfluramine (Fen-Phen) (Sept. 15, 1997), <http://www.fda.gov/cder/news/phen/fenphenpr81597.htm> (announcing withdrawal of Fen-Phen). The injuries associated with Fen-Phen resulted from a side effect that emerged only when two approved products were coadministered (an off-label use of each product). The name "Fen-Phen" referred to the combination of fenfluramine (or dexfenfluramine) and phentermine, briefly a widely prescribed weight-loss treatment. Each drug, used separately, had been found safe enough to win FDA approval, but in combination had the potential to cause heart valve damage. See generally Steven R. Salbu, *The FDA and Public Access to New Drugs: Appropriate Levels of Scrutiny in the Wake of HIV, AIDS, and the Diet Drug Debacle*, 79 B.U. L. REV. 93, 124–33 (1999) (describing approval and subsequent withdrawal of Fen-Phen).

<sup>51</sup> It is worth emphasizing that the problem with which this Note is concerned is not necessarily that an unstudied off-label use will *directly* injure consumers, because, for example, of a previously unidentified side effect that only manifests itself in the off-label context. Instead, this Note focuses on the problem of the unproven *effectiveness* of a drug for an off-label use—not necessarily that the product will affirmatively produce harmful effects, but that it will *not* produce its desired beneficial effects. This problem warrants independent consideration, in part because while adverse event reporting requirements currently exist to address the problem of side effects which become apparent only in the post-approval period, see Noah, *supra* note 50, at 468–81, there is no corresponding mechanism under the current regulatory system to identify off-label uses that are merely ineffective. However, even if an ineffective drug does not produce additional side effects, safety concerns are still implicated. Because the negative effects of a drug must be considered in light of its efficacy and the severity of the condition for which it is used, see *Benefit vs. Risk: How CDER Approves New Drugs*, in CTR. FOR DRUG EVALUATION & RESEARCH, FDA, FROM TEST TUBE TO PATIENT: IMPROVING HEALTH THROUGH HUMAN DRUGS 33, 33 (1999), <http://www.fda.gov/cder/about/whatwedo/testtube-5.pdf>, a drug may well be "safe" enough to approve for one use but not another. There is some inherent risk associated with the use of any biologically active compound, and there is no reason to expose patients to *any* potential harm unless there is some benefit—even a drug with relatively mild side effects might be considered unsafe if it produces negligible therapeutic benefit. In addition, the use of an ineffective treatment will, at least temporarily, preclude the use of other treatments which might prove effective. During this time, a patient may suffer unnecessarily, or the condition could become more severe or even untreatable.

<sup>52</sup> Before the Food, Drug, and Cosmetic Act (FD&C Act) was amended in 1962, the FDA only required that manufacturers give notice to the agency before bringing a product to market. The agency could then choose to delay the product's release pending further review of its safety. In the absence of any FDA action, perhaps due not to an informed assessment of the product's risks and benefits but instead to a lack of funding or manpower, the applicant would be permitted to sell the product sixty days after submission. Finding this notice system to be inadequate, and in the wake of Europe's tragic experience with thalidomide, a sedative drug responsible for thousands of "flipper limb" deformities in children born to mothers who had been prescribed the drug, Congress amended the

had to be assessed in the field by practitioners, unaided by data from well-designed clinical trials.<sup>53</sup> As proponents of EBM have pointed out, uncontrolled clinical observation is likely to yield inconclusive answers. Placebo effects and the possibility that a condition may improve in the absence of treatment seriously confound determinations of efficacy.<sup>54</sup> The task may be further complicated by the subtlety of a drug's effects, the difficulty in measuring these effects, and the fact that many effects will only become apparent over time. Therefore, the best way to arrive at answers regarding the safety and efficacy of a drug is through well-designed, properly controlled clinical trials.

## II

### PRODUCTION AND DISCLOSURE OF RESEARCH UNDER CURRENT LAW

#### A. *Weakness of Current Incentives to Study Off-Label Uses*

Because pharmaceutical manufacturers are not legally required to undertake research into off-label uses of their product, they will only do so if they believe this research will result in a net benefit to them. One important reason a manufacturer might be motivated to research an off-label use is to change a product's labeling information, in order to dispel physicians' doubts about efficacy or safety and encourage prescription for this (previously off-label) use.<sup>55</sup> A labeling change might be especially valuable to manufacturers because the FDA prohibits the manufacturer not only from mentioning unap-

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FD&C Act in 1962, changing the premarket *notice* system to a premarket *approval* system. See HARVEY TEFF & COLIN R. MUNRO, *THALIDOMIDE: THE LEGAL AFTERMATH* 1-6, 118-25 (1976); Merrill, *supra* note 22, at 1761-62.

<sup>53</sup> Without such evidence, physicians must rely on less reliable sources of information, including anecdotal reports, personal observations, intuition, and "N of 1 studies" (studies involving only a single patient). See generally Noah, *supra* note 6, at 402-06 (discussing methods of information transmission in medical community).

<sup>54</sup> Furthermore, patients using prescription drugs are likely to be in generally poor health and may therefore be at increased risk of additional health complications unrelated to their use of the drug. Cf. Kenneth J. Cooper, *Poor Patients Left with Little Choice: Informal Rationing Is Fact of Life at Public Clinic in North Carolina*, WASH. POST, May 2, 1994, at A1 (quoting public health clinic doctor who describes average patient suffering from diabetes, arthritis, and hypertension, and requiring more than three prescription drugs). They are also likely to be taking numerous medications or concurrently undergoing other types of treatment. See *id.* These factors likewise complicate attempts to draw a causal relationship between the drug and an adverse event.

<sup>55</sup> See, e.g., Thomas Bodenheimer, *Uneasy Alliance—Clinical Investigators and the Pharmaceutical Industry*, 342 NEW ENG. J. MED. 1539, 1541 (2000) (claiming that publication in prestigious journals influences physicians' prescribing habits).

proved uses on the product's labeling information,<sup>56</sup> but also from any promotion or advertisement of such uses.<sup>57</sup> FDA regulations even place limits on the degree to which a manufacturer may circulate published journal articles that pertain to off-label use.<sup>58</sup> Until recently, FDA prohibitions on circulation of information about off-label use were nearly absolute.<sup>59</sup> The Food and Drug Administration Modernization Act of 1997 (FDAMA) introduced a limited expansion of a manufacturer's ability to disseminate certain types of information to physicians.<sup>60</sup> Under the new rules, a manufacturer is permitted to distribute literature pertaining to off-label uses, but with some important restrictions that seriously reduce the value of this privilege.<sup>61</sup> Most importantly, in order to be eligible for these limited privileges, the manufacturer must be in the process of seeking supplementary approval for a labeling change, having at least made plans to complete the necessary trials to support the application.<sup>62</sup>

Therefore, a manufacturer could benefit from research undertaken in pursuit of a labeling change, both from the possibility of receiving the FDA's formal imprimatur with respect to the use in question, and from the ability to more freely promote and advertise such use under the provisions of the FDAMA. However, in order to qualify for either of these benefits, a manufacturer must seek a labeling change via the supplemental approval process. Supplemental approval requires submission of a Supplemental New Drug Application (SNDA),<sup>63</sup> the requirements of which are no less rigorous than

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<sup>56</sup> See 21 U.S.C. § 352(f) (2000) (providing that drug is "misbranded" if labeling does not include "adequate directions for use"); 21 C.F.R. § 201.5 (2004) (elaborating on what constitutes "adequate directions for use").

<sup>57</sup> See Prescription-Drug Advertisements, 21 C.F.R. § 202.1(e)(6) (2004); Thomas A. Hayes, *Drug Labeling and Promotion: Evolution and Application of Regulatory Policy*, 51 FOOD & DRUG L.J. 57, 57-62 (1996). The FD&C Act provides for sanctions, including criminal fines, imprisonment, and civil penalties, for violating the FDA's regulations on promotion of off-label use. See Weeks, *supra* note 42, at 662.

<sup>58</sup> A company cannot advertise or send unsolicited literature to physicians pertaining to unapproved uses, though it may send information in response to a physician's request. See Weeks, *supra* note 42, at 646-48.

<sup>59</sup> See *id.* at 647.

<sup>60</sup> Food and Drug Administration Modernization Act of 1997 (FDAMA), Pub. L. No. 105-115, § 401, 111 Stat. 2296, 2356-65 (codified as amended at 21 U.S.C. § 360aaa (2000)); see also Weeks, *supra* note 42, at 646-52.

<sup>61</sup> For example, a manufacturer may forward only unabridged peer-reviewed articles, clearly indicating that the use is unapproved and that the material is being distributed at the manufacturer's expense, disclosing any financial interests of the authors, and even including information on other products that have been approved for the same use. See Weeks, *supra* note 42, at 650-51.

<sup>62</sup> See 21 U.S.C. § 360aaa(b)(1)(A) (2000); Weeks, *supra* note 42, at 650.

<sup>63</sup> See 21 C.F.R. § 314.70 (2004).

those governing the original NDA.<sup>64</sup> While a manufacturer might be able to recycle some of the work previously submitted, it would be required to undertake the lengthy and expensive Phase 2 and Phase 3 trials to demonstrate "substantial evidence" of safety and effectiveness for this additional use.<sup>65</sup>

In addition to the expense of the studies themselves, there are other reasons to believe the financial return from a labeling change will be small. The effective patent life of a drug compound is already significantly shortened by the lengthy FDA approval process. Because of the additional time necessary for physicians to discover a potentially promising off-label use and to seek supplementary approval for this use, it is likely that the twenty years of market exclusivity conferred by a patent will have expired or be near expiration by the time a manufacturer could benefit from a successful SNDA.<sup>66</sup> Therefore, there will be at most a short period during which the manufacturer can collect monopoly profits from the newly-approved use of the drug. Furthermore, a manufacturer is able to collect profits from off-label prescriptions regardless of whether or not it pursues a labeling change, and it is likely difficult for a manufacturer to predict how much the formal addition of a previously off-label use in the labeling information would boost sales, when knowledge about the use has already spread throughout the medical community to some degree. The fact that a manufacturer was even considering research into off-label uses would indicate that such practice had become common enough for the manufacturer to take note. Because of greater ease and sophistication in the sharing of information in the electronic age, the informal channels of communication among doctors are likely to be much more effective than in previous eras. Accordingly, the manufacturer may play a less central role in circulating information about its products, and dissemination privileges may be of insufficient value to convince a manufacturer to undertake the research necessary to support a labeling change.<sup>67</sup>

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<sup>64</sup> See Weeks, *supra* note 42, at 655.

<sup>65</sup> See *id.*

<sup>66</sup> See 35 U.S.C. § 154(a)(2) (2000) (setting standard patent term at twenty years, measured from date of earliest filing); Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 156 (2000) (allowing patent term restoration of up to five years for drug patents to adjust for administrative delay, but capping extended patent term at fourteen years). The amount of time required for supplementary approval may be even longer than that required for initial approval, due to the fact that the FDA gives lower priority to the review of Supplemental New Drug Applications (SNDAs). See Weeks, *supra* note 42, at 662–63.

<sup>67</sup> See Weeks, *supra* note 42, at 662–63 (discussing balance of costs and benefits of seeking FDAMA dissemination privileges to manufacturer).

Given the unappealing prospect of essentially repeating the NDA process in order to gain approval for an additional use, the rather limited privileges available under FDAMA, and the small additional profits to be gained from a labeling change, it seems unlikely that many manufacturers will choose to pursue supplementary approval for off-label uses of their drugs.<sup>68</sup> While some incentives may exist for manufacturers to conduct research into off-label uses, it is clear that these incentives are not particularly reliable. When profits are not likely to be increased or when the outcome of the research is uncertain, it will not be in a manufacturer's interests to carry out post-approval research. Similarly, while the benefits of advertising or expanded dissemination privileges might in some cases be sufficient to bring about such action, this will not always be true. As a result, much of the research that would permit physicians to employ an evidence-based approach in their off-label prescription choices is likely not to be undertaken.

### *B. Legal Obstacles to Disclosure of Research Findings*

In light of the questionable incentives for manufacturers to conduct research into the efficacy of their products for off-label uses, it would seem reasonable to impose some type of affirmative obligation on manufacturers to produce such research. Indeed, this has been done on a limited scale as part of the Best Pharmaceuticals for Children Act (BPCA),<sup>69</sup> discussed below in Part III. However, even if such an obligation were in place, an overlapping and equally important problem would remain. In addition to ensuring that research is produced, any worthwhile solution to the lack of data on the efficacy of off-label treatments must also provide for the *disclosure* of the research findings, reported accurately and in a form that is readily accessible and useful to the medical community.

The problem is illustrated by the recent controversy over the safety of selective serotonin reuptake inhibitors (SSRIs), a widely prescribed class of antidepressant drugs.<sup>70</sup> In most cases, prescription of SSRIs for use in children is off-label because the drugs have been

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<sup>68</sup> See *id.* An additional reason manufacturers might be reluctant to seek dissemination privileges under FDAMA is that participation in this program would result in increased FDA scrutiny of the manufacturer's activities, and a higher likelihood that sanctions would be imposed. See *id.* at 662.

<sup>69</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.).

<sup>70</sup> These drugs (with manufacturers) include Paxil (GlaxoSmithKline), Effexor (Wyeth), Prozac (Eli Lilly), Celexa (Forest Laboratories), Lexapro (Forest Laboratories), Luvox (Solvay), and Zoloft (Pfizer). See Harlan Spector, *Anti-Depressants for Kids: Life-saver or Suicide Risk?*, PLAIN DEALER (Cleveland), Mar. 11, 2004, at F1.

approved for use in adults only.<sup>71</sup> Patients' advocates organizations have claimed that manufacturers of these drugs have conducted studies to investigate the effects of these drugs in children, and have never published or otherwise announced the results.<sup>72</sup> These accusations have been made in the context of an ongoing debate about the safety of these drugs, particularly their potential to produce suicidal thoughts and behavior in a subset of users.<sup>73</sup> The results of these studies have not been made public, critics suggest, because the data would show the drugs to be ineffective.<sup>74</sup> If these allegations are true, then use of these drugs in children, for whom they have been widely prescribed,<sup>75</sup> would expose them to the risk of a life-threatening side effect without any corresponding benefit.

Such a failure to provide a full and complete picture of a drug's efficacy is worrisome, most obviously because without disclosure, these findings cannot inform physicians' prescription practices. Perhaps more troubling is the possibility that favorable results will be published and unfavorable results suppressed; this practice may lead to erroneous reliance by physicians consulting this literature and assuming it to be complete and reliable. That is, when selective publi-

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<sup>71</sup> Fluoxetine (Prozac), sold by Eli Lilly, is the only SSRI that is approved by the FDA for use by persons under eighteen. *See id.*

<sup>72</sup> *See* Shankar Vedantam, *Antidepressant Makers Withhold Data on Children*, WASH. POST, Jan. 29, 2004, at A1 (describing drug industry's efforts to suppress data from clinical trials involving depressed children).

<sup>73</sup> *See* Diaz, *supra* note 12, at 87–92 (discussing studies suggesting association between use of SSRIs and increased rates of suicide and suicide attempts); Jonathan Mahler, *The Antidepressant Dilemma*, N.Y. TIMES, Nov. 21, 2004, § 6 (Magazine), at 59 (discussing link between SSRIs and “suicide ‘ideation,’ or suicidal thoughts, in adolescents” and drug companies’ withholding of data from clinical trials).

<sup>74</sup> *See* Laurence Greenhill, Chairman, Am. Acad. of Child & Adolescent Psychiatry Pediatric Psychopharmacology Initiative, *Statement from the American Academy of Child and Adolescent Psychiatry for the Food and Drug Administration Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee on Child and Adolescent Suicidality and Anti-Depressant Drugs* (Feb. 2004), <http://www.aacap.org/Announcements/March2004FDA.htm> (reporting that sixteen of twenty studies mentioned in recent FDA publications are treated as proprietary data and trade secrets, and remain unpublished); Vedantam, *supra* note 72, at A1 (“Researchers familiar with the unpublished data said the majority of secret trials show that children taking the medicines did not get any better than children taking dummy pills.”); Shankar Vedantam, *Drugmakers Prefer Silence on Test Data: Firms Violate U.S. Law by Not Registering Trials*, WASH. POST, July 6, 2004, at A1 [hereinafter Vedantam, *Drugmakers*] (suggesting that selectively published research on antidepressants may have misrepresented their effectiveness in children). *But see* Spector, *supra* note 70, at F1 (quoting psychiatrist who points out that physicians familiar with data continue to prescribe SSRIs for children).

<sup>75</sup> *See* Ronald Kotulak, *False Alarm and Need to Know: Media and Science at Odds Over News, Timing, Values*, CHI. TRIB., Apr. 4, 2004, § 2, at 1 (reporting that one to two million children receive SSRIs).



cation is possible, the impression emerging from the published literature will overstate the true efficacy of the drug, and a physician may place more confidence in a treatment based on this literature, unaware that other studies exist that would call that conclusion into question.<sup>76</sup> An incomplete body of data like that which would result from selective publication could seriously impair a physician's attempt to evaluate meaningfully the costs and benefits of a treatment.

### 1. *Disclosure by Academic Researchers*

Though there is no existing legal obligation for manufacturers to disseminate the results of their research, and though manufacturers are not likely to voluntarily publicize results unfavorable to their products,<sup>77</sup> there are other channels through which this information might reach the public. These alternatives should be considered before concluding that legislative or regulatory action is necessary. First, when pharmaceutical manufacturers conduct the large-scale clinical trials that are required to win FDA approval for a product, they must enlist outside help from researchers with access to clinical populations.<sup>78</sup> Traditionally, manufacturers have made arrangements with academic medical centers;<sup>79</sup> physician-researchers at these institutions would design the study, implement the study protocol, and collect the data.<sup>80</sup> Given the researchers' important role in conducting the study and their interest in publishing the results to advance their own careers,<sup>81</sup> they might reasonably expect to participate in the analysis of the data and the decision concerning whether and what to publish. However, manufacturers have frequently attempted to assert control over the information produced by this research through con-

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<sup>76</sup> In a clinical trial, the assessment of a drug's effectiveness is based upon the statistical significance of its effect on some outcome or clinical marker appropriate to measure the medical benefit it is claimed to provide. See Larry R. Versteegh, *Science and Regulatory Rituals Associated With the Drug Development Process*, 52 FOOD & DRUG L.J. 155, 157-58 (1997) (describing statistical measure applied by FDA). A statistically significant effect, by convention, is defined as an effect that is at least ninety-five percent likely not to have occurred due to chance alone. See *id.* at 157. The existence of negative studies might suggest that the positive result was due to chance, that it is particularly sensitive to testing conditions, or that the effect, while real, is weaker than the positive result viewed in isolation would suggest.

<sup>77</sup> Interestingly, while manufacturers are required to disclose the existence of certain clinical trials in a government database, the law containing this requirement includes no mechanism for enforcement and has been frequently ignored by manufacturers. See Vedantam, *Drugmakers*, *supra* note 74, at A1.

<sup>78</sup> See Bodenheimer, *supra* note 55, at 1539-40.

<sup>79</sup> See *id.*

<sup>80</sup> See *id.*

<sup>81</sup> See *id.* at 1541 ("For academic investigators, publication in peer-reviewed journals is the coin of the realm.").

tractual provisions that restrict the researchers' freedom to publish or to access the complete data without permission of the manufacturer sponsor.<sup>82</sup>

Academic researchers, predictably, have resisted these provisions; many conflicts between investigators and their industry sponsors have been reported.<sup>83</sup> The medical community has spoken out against these restrictions, and major medical journals have adopted policies that require submitting authors to attest that they had access to all data and control over the decision to publish.<sup>84</sup> However, for a number of reasons, academic researchers may lack the negotiating strength to force manufacturers to change their practice in this area. First, medical research is often dependent upon industry funding, and researchers may be understandably concerned about damaging their relationships with the industry.<sup>85</sup> Perhaps more importantly, academic researchers and institutions probably do not have the same willingness, time, or money to engage in prolonged legal battles as does a pharmaceutical company, for which this may simply be a "cost of doing business."<sup>86</sup> Finally, in recent years, private for-profit research companies have emerged, often managing pharmaceutical clinical trials faster and with less hassle, from the manufacturers' perspective, than academic medical centers.<sup>87</sup> The emergence of this commercial alternative may cause academic researchers to accede more readily to industry's terms on disclosure of and control over clinical trial data, especially because their private competitors are unlikely to insist on such privileges themselves.<sup>88</sup>

## 2. *FDA Disclosure via the Freedom of Information Act*

Another possible route for disclosure is through the FDA. Though it does not impose any disclosure or publication obligations on manufacturers, the agency does require regular submissions of information regarding a manufacturer's post-approval activities. A

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<sup>82</sup> If data are gathered from multiple testing sites, for example, researchers at one testing site may not have access to the data from other sites without the cooperation of the sponsor. See Patricia Baird, *Getting It Right: Industry Sponsorship and Medical Research*, 168 CAN. MED. ASS'N J. 1267, 1267 (2003) (noting recent survey showing only one percent of medical school researchers had access to all clinical trial data); Bodenheimer, *supra* note 55, at 1541 (noting delays and restrictions in publishing).

<sup>83</sup> See Bodenheimer, *supra* note 55, at 1541–42 (discussing cases where manufacturers blocked or delayed publication of research results).

<sup>84</sup> See Frank Davidoff et al., *Sponsorship, Authorship, and Accountability*, 165 CAN. MED. ASS'N J. 786, 786–88 (2001).

<sup>85</sup> See Baird, *supra* note 82, at 1267.

<sup>86</sup> See *id.*

<sup>87</sup> See Bodenheimer, *supra* note 55, at 1539–40.

<sup>88</sup> See *id.* at 1542.

manufacturer must receive an IND exception before its drug can be administered to patients as part of a clinical trial;<sup>89</sup> this requirement applies regardless of whether or not the manufacturer intends to apply for a labeling change.<sup>90</sup> A manufacturer that sought supplementary approval for its drug and opted to use post-approval research to support an SNDA would need to submit “full reports” from this research.<sup>91</sup> As a result, a company choosing not to seek FDA approval for off-label uses would not be required to submit the “full reports,” but still would be under an obligation to report certain information to the FDA.<sup>92</sup> Therefore, even if no affirmative public disclosure obligation applies to post-approval research, the manufacturer will still be required to reveal some of the resulting information to the FDA.

Given its role as guardian of public health,<sup>93</sup> it might be expected that the FDA, when in possession of information pertaining to the

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<sup>89</sup> Because it is not generally recognized “as safe and effective,” an off-label use is considered to be a “new drug” under the FD&C Act. See 21 U.S.C. § 321(p)(1) (2000) (defining “new drug” as “[a]ny drug . . . not generally recognized, among experts qualified by scientific training and experience . . . as safe and effective for use under the condition prescribed, recommended, or suggested in the labeling thereof”). However, an IND arguably might not be required before undertaking clinical trials investigating an off-label use. See, e.g., Karen J. Cooper, *Pediatric Marketing Exclusivity—As Altered by the Best Pharmaceuticals for Children Act of 2002*, 57 FOOD & DRUG L.J. 519, 543 (2002) (treating as unresolved question whether IND would be required for pediatric studies of marketed drugs approved for adults). There is an exception to the IND requirement for investigations not intended for use in support of an application for a new indication or significant change in labeling. See 21 C.F.R. § 312.2(b) (2004). If a company did not seek to use the study for this purpose and could meet the other requirements, it might not be required to submit an IND. See *id.* (listing other exemption requirements). However, in order to reserve for itself the possibility of using the study as part of a later NDA or SNDA, and in order to avoid potential problems with the FDA, a manufacturer is likely to acquire an IND before conducting such research. E-mail from Lars Noah, Professor of Law, University of Florida College of Law, to Author (Apr. 19, 2004, 20:29:46 EST) (on file with author). It is somewhat ironic that permission is required in order to conduct a formal clinical trial in which patients will receive a drug off-label, while physicians may engage in much more haphazard experimentation on their patients without constraints. See, e.g., Noah, *supra* note 46, at 399–400.

<sup>90</sup> A manufacturer might choose to undertake studies even though it does not seek a labeling change in order to insert information about the off-label use into the medical literature, which may help to increase the acceptance of an off-label use even in the absence of FDAMA dissemination privileges.

<sup>91</sup> See *supra* text accompanying notes 30–35.

<sup>92</sup> See 21 C.F.R. § 312.33 (2004) (requiring annual reports from IND recipient with “brief summary” of any studies underway or completed, including information on adverse experiences and “brief description of any available study results”).

<sup>93</sup> See FDA, Dep’t of Health & Human Servs., FDA’s Mission Statement, <http://www.fda.gov/opacom/morechoices/mission.html> (last visited Apr. 15, 2005) (“The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human . . . drugs . . . and helping the public get the accurate, science-based information they need to use medicines . . . to improve their health.”).

efficacy of off-label uses, would make appropriate disclosures in the public interest. Furthermore, the FDA may be subject to the mandatory disclosure provisions of the Freedom of Information Act (FOIA),<sup>94</sup> enacted for the purpose of increasing the transparency of agency operation.<sup>95</sup> The FOIA mandates the disclosure, either routinely or upon request, of all agency records unless such records fall within an exempted category of information.<sup>96</sup> Historically, the FDA has claimed that the FOIA does not apply to clinical trial data in its possession (e.g., information submitted as part of an NDA) because it falls within Exemption 4, which creates exceptions for “trade secrets” and for “commercial or financial information . . . [that is] privileged or confidential.”<sup>97</sup> The “trade secret” prong of Exemption 4 has been construed narrowly by courts interpreting the FOIA, requiring a “direct relationship between the information at issue and the productive process.”<sup>98</sup> At least one court has concluded without difficulty that “health and safety data” do not fall within this definition.<sup>99</sup>

However, a stronger case can be made that research data fall within the broader confidential commercial information prong of Exemption 4. Because health and safety data are a required component in the drug approval process, these satisfy the “commercial” requirement.<sup>100</sup> Information is considered to be “confidential” for purposes of the statutory language if disclosure by the agency would “(1) . . . impair the Government’s ability to obtain necessary information in the future; or (2) . . . cause substantial harm to the competitive

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<sup>94</sup> Freedom of Information Act (FOIA), 5 U.S.C. § 552 (2000).

<sup>95</sup> See Stephen R. Wilson, *Public Disclosure Policies: Can a Company Still Protect Its Trade Secrets?*, 38 NEW ENG. L. REV. 265, 280–81 (2004).

<sup>96</sup> 5 U.S.C. § 552(a)–(b) (2000).

<sup>97</sup> 5 U.S.C. § 552(b)(4); see also Roberta Schugmann & Leslie Shaw, *The Application of Trade Secret Protection to Safety and Effectiveness Data of Patented Drugs*, 16 U.C. DAVIS L. REV. 463, 475 (1983) (questioning FDA’s interpretation of this exemption); Barry Meier, *F.D.A. Will Not Release Some Data on Heart Devices*, N.Y. TIMES, Aug. 6, 2005, at C3 (discussing FDA’s refusal to release information on frequency and cause of heart device failure in response to FOIA request, claiming such information exempted as “a corporate trade secret”).

<sup>98</sup> Pub. Citizen Health Research Group v. FDA, 704 F.2d 1280, 1288 (D.C. Cir. 1983). The court defined “trade secret” as “a secret, commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort.” *Id.*

<sup>99</sup> See *id.* at 1287.

<sup>100</sup> *Id.* at 1290 (“Because documentation of the health and safety experience of their products will be instrumental in gaining marketing approval for their products, it seems clear that the manufacturers . . . have a commercial interest in the requested information.”).

position of the person from whom the information was obtained.”<sup>101</sup> When information has been given to the FDA involuntarily, as is the case with information submitted as a condition of FDA approval,<sup>102</sup> there is deemed to be no potential impairment of the agency’s ability to collect the information.<sup>103</sup> However, to meet the second, “substantial harm” requirement, a showing of *actual* competitive harm is not required.<sup>104</sup> Instead, the party opposing disclosure need only show that the submitter of the information actually faces competition, and that “substantial competitive injury would likely result from disclosure.”<sup>105</sup>

The question whether information qualifies as confidential commercial information is necessarily highly fact-dependent and must be determined on a case-by-case basis; it is difficult to draw general conclusions from the opinions, which necessarily do not detail exactly what sort of confidential material is at issue.<sup>106</sup> The legal doctrine in this area, therefore, might not definitively preclude the possibility that safety and efficacy data might be subject to disclosure. Nonetheless, the FDA has not generally pursued a pro-disclosure policy,<sup>107</sup> and

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<sup>101</sup> *Nat’l Parks & Conservation Ass’n v. Morton*, 498 F.2d 765, 770 (D.C. Cir. 1974) (footnote omitted). The competitive harm referred to here is limited to harm caused by a competitor’s use of the information in question. For example, it does not include “customer or employee disgruntlement” or “embarrassing publicity.” *Pub. Citizen Health Research Group*, 704 F.2d at 1291 n.30 (quoting Mark Q. Connelly, *Secrets and Smoke-screens: A Legal and Economic Analysis of Government Disclosures of Business Data*, 1981 WIS. L. REV. 207, 235–36); see also *Pub. Citizen Health Research Group v. FDA*, 185 F.3d 898, 903–04 (D.C. Cir. 1999) (holding that public benefit of disclosure is not to be considered in this analysis); Charles N. Davis, *A Dangerous Precedent: The Influence of Critical Mass III on Exemption 4 of the Federal Freedom of Information Act*, 5 COMM. L. & POL’Y 183, 196 (2000) (discussing *Critical Mass III* case which creates new standard for withholding of information submitted voluntarily, granting agency more discretion to withhold).

<sup>102</sup> See, e.g., *Pub. Citizen Health Research Group v. FDA*, 964 F.Supp. 413, 414 n.1 (D.D.C. 1997) (finding submission of information related to required postmarketing study to be involuntary).

<sup>103</sup> See *Morton*, 498 F.2d at 770.

<sup>104</sup> *Pub. Citizen Health Research Group*, 704 F.2d at 1290–91.

<sup>105</sup> *Nat’l Parks & Conservation Ass’n v. Kleppe*, 547 F.2d 673, 679 (D.C. Cir. 1976). This showing is typically made by way of affidavits from company officials or qualified experts. See Stephen Gidiere & Lawrence P. Mellinger, *Stemming the Release of Commercially Valuable Information Under FOIA*, 16 NAT. RESOURCES & ENV’T 288, 326–27 (2001).

<sup>106</sup> See, e.g., *Pub. Citizen Health Research Group*, 185 F.3d 898; *Anderson v. Dep’t of Health & Human Servs.*, 907 F.2d 936 (10th Cir. 1990); *Pub. Citizen Health Research Group*, 704 F.2d 1280; *Pub. Citizen Health Research Group*, 964 F. Supp. 413; *Citizens Comm’n on Human Rights v. FDA*, No. 92CV5313, 1993 WL 1610471 (C.D. Cal. 1993).

<sup>107</sup> See generally James T. O’Reilly, *Knowledge Is Power: Legislative Control of Drug Industry Trade Secrets*, 54 U. CIN. L. REV. 1 (1985) (providing background and context of FDA policies toward information disclosure up to 1985). This has not always been true. There was at one time a sentiment within the agency that more industry data should be made publicly available. See *id.* at 11–13.

courts have frequently upheld FDA conclusions that information requested under the FOIA is exempted from disclosure.<sup>108</sup> In addition, the case-by-case analysis necessary in determining the appropriate treatment of particular information leads to considerable legal uncertainty surrounding the likelihood of success in litigation; this may dissuade requesting parties from challenging agency decisions to withhold information.<sup>109</sup>

The FOIA exemptions only release an agency from the *mandatory* disclosure obligation imposed by the FOIA. Neither the exemptions nor any other provision of the FOIA would prevent the FDA from disclosing exempted information at its discretion. However, there are overlapping legal restrictions on an agency's discretion to release information to the public. For example, the Trade Secrets Act<sup>110</sup> (TSA) criminalizes agency release of a broad category of information received from regulated businesses.<sup>111</sup> Because the TSA has been interpreted as "at least co-extensive" with the classes of information addressed by Exemption 4 of the FOIA,<sup>112</sup> it prohibits the FDA from disclosing this information whenever the FOIA does not apply. Even in the absence of these criminal sanctions, disclosure by any FDA employee of trade secrets or "confidential commercial or financial information" is affirmatively prohibited by the FDA's own regulations.<sup>113</sup> Therefore, though the FOIA exemptions would allow the FDA to disclose these categories of information at its discretion, this discretion is not available to the FDA in practice due to the other legal obstacles prohibiting disclosure of research data.

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<sup>108</sup> See, e.g., *Pub. Citizen Health Research Group*, 185 F.3d at 903, 905–06 (ruling that FDA was not required, in response to FOIA request, to disclose safety and efficacy data from INDs and NDAs containing "privileged or confidential" commercial information). *But see* *Teich v. FDA*, 751 F.Supp. 243, 245 (D.D.C. 1990) (requiring disclosure of animal studies submitted to FDA as part of application for approval of silicone gel breast implant products).

<sup>109</sup> Cf. Jay L. Koh, *From Hoops to Hard Drives: An Accession Law Approach to the Inevitable Misappropriation of Trade Secrets*, 48 AM. U. L. REV. 271, 286–88 (1998) (arguing that case-by-case approach leads to uncertainty concerning outcome of litigation and may favor party seeking nondisclosure of trade secrets).

<sup>110</sup> 18 U.S.C. § 1905 (2000).

<sup>111</sup> The Trade Secrets Act (TSA) prohibits the disclosure by an agency employee of "any information . . . concern[ing] or relat[ing] to the trade secrets, processes, operations, style of work, or apparatus, or to the identity, confidential statistical data, amount or source of any income, profits, losses, or expenditures of any person, firm, partnership, corporation, or association." *Id.*

<sup>112</sup> *CNA Fin. Corp. v. Donovan*, 830 F.2d 1132, 1151 (D.C. Cir. 1987); see also 37A AM. JUR. 2D *Freedom of Information Acts* § 176 (1994) (discussing relationship of TSA to FOIA Exemption 4).

<sup>113</sup> 21 C.F.R. § 20.61(c) (2004) ("Data and information submitted or divulged to the Food and Drug Administration which fall within the definitions of a trade secret or confidential commercial or financial information are not available for public disclosure.").

## III

## POLICY CONSIDERATIONS AND POTENTIAL SOLUTIONS

A. *The Competitive Value of Clinical Research Data: Is Significant Harm Likely to Result from Disclosure?*

In considering the appropriateness of categorizing clinical research data as a trade secret or as confidential commercial information for the purposes of the FOIA and other legal barriers to disclosure, it is necessary to consider what consequences would result from disclosure. Commentators have pointed out that, especially in the electronic age, the FOIA raises serious concerns for parties that are required to turn over information to government agencies.<sup>114</sup> Indeed, in the FDA context, one commentator has asserted that “[t]he FDA possesses among its routinely collected files some of the most sensitive nonmilitary data in the whole universe of federal records.”<sup>115</sup> If information is commercially valuable to competitors, and disclosure allows them to “free-ride” on an innovator’s investment, this would constitute competitive harm, and would have important consequences for investment in innovation in pharmaceutical products.<sup>116</sup>

It is certainly possible that manufacturers are disingenuous in their arguments that competitive harm would result from disclosure of research data and are simply seeking to retain the ability to suppress unfavorable results. However, if there is a legitimate competitive interest worth protecting in this type of information, any solution that aims to guarantee disclosure of research findings must be crafted so as to protect this interest adequately. It is therefore necessary to examine more closely the type of information at issue, and the actual risks in its disclosure.

While much of the material submitted to the FDA clearly contains sensitive and commercially valuable information, it is necessary to distinguish different types of information, submitted in different

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<sup>114</sup> See Gidiere & Mellinger, *supra* note 105, at 288. The Electronic Freedom of Information Act Amendments of 1996 (E-FOIA), Pub. L. No. 104-231, 110 Stat. 3048 (codified as amended at 5 U.S.C. § 552 (2000)), made several significant changes to the FOIA, including the requirement that agencies establish so-called “electronic reading rooms”—websites containing documents that “the agency determines have become or are likely to become the subject of subsequent requests.” 5 U.S.C. § 552(a)(2)(D)–(E) (2000); see also Gidiere & Mellinger, *supra* note 105, at 288 (describing “electronic reading rooms”); Thomas O. McGarity & Sidney A. Shapiro, *The Trade Secret Status of Health and Safety Testing Information: Reforming Agency Disclosure Policies*, 93 HARV. L. REV. 837, 848–56 (1980) (discussing arguments against disclosure of health and safety data).

<sup>115</sup> 1 JAMES T. O'REILLY, *FEDERAL INFORMATION DISCLOSURE* § 14:92 (3d ed. 2000).

<sup>116</sup> See, e.g., McGarity & Shapiro, *supra* note 114, at 850 (noting concern that disclosure could “lead to a [competitor’s] breakthrough that would undermine the ability of the original innovator to reap the benefits of its innovation”).

contexts, and for different purposes. The appropriateness of confidentiality versus disclosure depends crucially upon the particular type of information in question. An NDA, which contains virtually everything known about a valuable and still-unmarketed product, is likely to include much sensitive information.<sup>117</sup> In contrast, a disclosure limited to data from clinical trials investigating off-label uses seems to pose a much weaker case for confidentiality. Since the product is already on the market, trade secrets relevant to earlier stages of the development process (e.g., information relating to formulation or the manufacturing process) are not likely to be at issue. The information that is of immediate importance to the public is that to be gained from access to clinical research data addressing the efficacy of a product that is presently being prescribed by physicians and used by consumers.

Previous discussions of the problem of FDA disclosure of research data have focused primarily on the competitive harm resulting from generic competitors.<sup>118</sup> A generic manufacturer is one that seeks to market products that are chemically identical to drugs that have already received FDA approval.<sup>119</sup> By contrast, the “pioneer” manufacturer is the one that has invested the time and money in research and development necessary to receive FDA approval for a novel pharmaceutical product.<sup>120</sup> Clearly, incentives for pioneer firms to invest in the development of new drugs would be diminished if generic manufacturers were able to appropriate pioneers’ data freely to support their own NDAs, perhaps at the negligible cost of a FOIA request, obviating the time and expense required to duplicate these results.<sup>121</sup>

This particular concern could be addressed directly by disallowing the unauthorized use of another’s data.<sup>122</sup> Indeed, Congress, in an attempt to balance the interests of generic and pioneer firms, has addressed the use of pioneer data by generic competitors with the

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<sup>117</sup> In *Anderson v. Department of Health & Human Services*, the court listed a number of categories used by the FDA in justifying its refusal to release information from an NDA, based on Exemption 4 of the FOIA. 907 F.2d 936, 940 (10th Cir. 1990). These included “[m]anufacturing and processing information, including formulations, chemistry and quality assurance procedures”; “[p]rotocols”; “[p]reclinical test data”; “[c]linical test data”; “[p]atient information”; and “[m]arketing, sales and customer information.” *Id.*

<sup>118</sup> See, e.g., McGarity & Shapiro, *supra* note 114, at 848–56; O’Reilly, *supra* note 107, at 2–7, 23–24.

<sup>119</sup> See Elizabeth Stotland Weiswasser & Scott D. Danzis, *The Hatch-Waxman Act: History, Structure, and Legacy*, 71 ANTITRUST L.J. 585, 585 (2003).

<sup>120</sup> See *id.*

<sup>121</sup> See O’Reilly, *supra* note 107, at 4–5 (noting that market exclusivity provides return necessary to compensate for millions of dollars invested in obtaining FDA approval).

<sup>122</sup> See McGarity & Shapiro, *supra* note 114, at 849 n.59.



Hatch-Waxman Act of 1984 (Hatch-Waxman).<sup>123</sup> Hatch-Waxman creates a system which allows generic companies to rely upon a pioneer's data, but with restrictions intended to guarantee that the pioneer is able to profit appropriately from its product.<sup>124</sup> FDA regulations specifically prohibit the unauthorized use of another's data outside the Hatch-Waxman framework.<sup>125</sup>

However, procedures for market approval in foreign countries may not include these same limitations.<sup>126</sup> It has been claimed that licensing of safety and effectiveness data to competitors might be an important source of the financial return expected from a drug.<sup>127</sup> In a country where Hatch-Waxman-type restrictions are not in place, an innovator might suffer legitimate competitive harm if data were released that could be used by a generic competitor in support of approval, because this would eliminate the possibility for the pioneer to collect licensing revenue from these data. However, the FDA already routinely releases data summaries without crippling effects on innovation,<sup>128</sup> and it would seem that a properly crafted disclosure rule could adequately protect the interests of the innovator firms.<sup>129</sup> Notably, some economic studies have called into question the significance of the harm from an appropriation of a competitor's data to support a foreign application for approval.<sup>130</sup> Even if disclosure might currently result in some competitive harm, this harm may be decreased in the future as international standards for drug approval are harmonized.<sup>131</sup> As the Hatch-Waxman compromise illustrates,

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<sup>123</sup> Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of 21 U.S.C. and 35 U.S.C.).

<sup>124</sup> The Hatch-Waxman Act of 1984 (Hatch-Waxman) allows generic drugs to come to market based upon a showing of bioequivalence to an FDA-approved product. In order to compensate pioneer manufacturers for the increased competition that would result from generic entry into the market, patent terms on pharmaceutical products were effectively extended by awarding periods of market exclusivity for novel products. See Weiswasser & Danzis, *supra* note 119, at 585, 590-91.

<sup>125</sup> See 21 C.F.R. § 314.50(g)(1), (3) (2004).

<sup>126</sup> See McGarity & Shapiro, *supra* note 114, at 849-50 (discussing possibility of firm using competitor's information to obtain approval in foreign markets); O'Reilly, *supra* note 107, at 7 n.31 (same).

<sup>127</sup> See O'Reilly, *supra* note 107, at 23 & n.134.

<sup>128</sup> See 21 C.F.R. § 314.430(e)(2) (2004) (requiring public disclosure of summaries of all "safety and effectiveness data" unless "extraordinary circumstances exist").

<sup>129</sup> See McGarity & Shapiro, *supra* note 114, at 876-82 (discussing compensation scheme to remedy harm resulting from disclosure of health and safety data and identifying numerous problems with this approach).

<sup>130</sup> See *id.* at 853 (quoting economist who found industry estimates of harm to be "a gross overstatement").

<sup>131</sup> See generally Joseph G. Contrera, Comment, *The Food and Drug Administration and the International Conference on Harmonization: How Harmonious Will International Phar-*

there also may be alternative means of protecting innovators' interests.<sup>132</sup>

Since Hatch-Waxman has resolved most of the important issues regarding generic firms' use of clinical trial data, the primary competitive harm that is likely to follow from disclosure of valuable information in the current environment comes not from generic competition, but from competitors that seek to develop "follow-on" or "me too" products. A "follow-on" drug is one that is similar, in chemical structure or mechanism of action, to the drug to which the disclosed clinical data relate.<sup>133</sup> Because the competitor firm will be seeking approval for a non-identical product, the innovator's data could not be used in support of a follow-on NDA or SNDA. Any unapproved compound is a "new drug," and three phases of human clinical trials will be required to establish its safety and efficacy, regardless of whether other chemically similar drugs have already received approval.<sup>134</sup>

It might be particularly worthwhile for a competitor to seek to develop a follow-on drug for many reasons.<sup>135</sup> First, such an approach minimizes the considerable risk normally involved in drug development. The knowledge that a related compound has successfully survived the FDA approval process gives a manufacturer greater confidence, though by no means certainty, that its follow-on product will also receive approval, and therefore, that its research and development expenses will not have been wasted on a product that does not reach market.<sup>136</sup> Furthermore, a follow-on competitor might expect that the FDA will subject its product to a lower level of scrutiny, and will grant approval more quickly and at lower cost.<sup>137</sup> After

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*maceutical Regulations Become?*, 8 ADMIN. L.J. AM. U. 927 (1995) (discussing harmonization of drug approval regimes internationally).

<sup>132</sup> See *supra* note 124.

<sup>133</sup> See Joseph A. DiMasi & Cherie Paquette, *The Economics of Follow-on Drug Research and Development: Trends in Entry Rates and the Timing of Development*, 22 PHARMACOECONOMICS 1, 2 (Supp. 2, 2004) (discussing follow-on drugs), available at [http://www.who.int/intellectualproperty/submissions/en/Submission\\_DiMasi.pdf](http://www.who.int/intellectualproperty/submissions/en/Submission_DiMasi.pdf).

<sup>134</sup> See *supra* notes 22–29 and accompanying text.

<sup>135</sup> Cf. DiMasi & Paquette, *supra* note 133, at 5–7 (listing seventy-two therapeutic classes of drugs in which follow-on drug development has taken place).

<sup>136</sup> It has been estimated that only twenty percent of drugs for which an IND is received will ultimately be approved for public use. See 1 O'REILLY, *supra* note 32, § 13:11.

<sup>137</sup> Information relating to a testing protocol could also be valuable to a competitor. For example, a competitor might want to copy a study design that was successfully used to gain approval for a novel use, or to avoid one that proved not to be fruitful. However, a competitor subsequently pursuing its own NDA or SNDA will likely benefit from its predecessors' experiences even without disclosure, because trials are designed in close coordination with FDA officials, who are unlikely to withhold useful design ideas that emerged during the course of testing for a related drug. See Merrill, *supra* note 22, at 1778–79 (discussing FDA's involvement in design and recordkeeping of clinical studies).

a related drug's approval, the competitor may also encounter less difficulty convincing the medical establishment of the drug's usefulness compared to existing treatments, since positive experience with a related drug may help to break down any initial resistance of physicians to an unfamiliar treatment option.<sup>138</sup>

A disclosure concerning the efficacy of an approved drug for an off-label use could similarly benefit competitors due to the "intelligence value" it conveys.<sup>139</sup> The competitor might use this information to decide whether to invest in similar trials for an approved follow-on product. If the product has not yet been approved, the competitor could use the information to decide whether to attempt to gain formal approval for additional uses as part of its initial NDA. In either case, the competitor arguably benefits unfairly from its predecessor's efforts.

Here, as in the generic context, however, the reality and importance of the competitive harm that the pioneer company will suffer from disclosure is questionable. It is not at all clear that the knowledge that a similar product was effective or ineffective in treating some condition would have any effect on a follow-on competitor's decision to undertake similar studies. Though two drugs may share common structures and/or mechanisms of action, small structural differences may have dramatic consequences for the drug's ability to bind to a particular receptor and produce physiological effects.<sup>140</sup> As a result, the relative balance between side effects and main effects for two similar drugs may be quite different. Therefore, a finding of safety and efficacy for one compound would still require confirmation for a similar one. Likewise, a negative finding, rather than indicating the likely failure of a similar product, may instead signal an opportunity to exploit a market that a competitor cannot.<sup>141</sup>

For the reasons discussed above, the reality of the competitive harm issuing to pharmaceutical makers due to disclosure of clinical data is questionable, particularly with respect to research in the post-approval period. The potential for harm from generic firms has been minimized by Hatch-Waxman, while that from non-generic firms seems largely speculative. The fact that it is in a manufacturer's

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<sup>138</sup> See Noah, *supra* note 50, at 496 (noting common physician preference for drugs "with a more developed safety profile").

<sup>139</sup> See McGarity & Shapiro, *supra* note 114, at 883-84.

<sup>140</sup> See JULIEN, *supra* note 13, at 38.

<sup>141</sup> While disclosure of a deficiency in a product might lead to competitive harm, this seems a proper and desirable basis for market competition. See Robert G. Vaughn, *Consumer Access to Product Safety Information and the Future of the Freedom of Information Act*, 5 ADMIN. L.J. 673, 682 (1991).

interest to publish research results voluntarily when the results are favorable to its product suggests either that the risk of harm has been exaggerated or that it is possible to communicate the results to the medical community without divulging sensitive information. In any case, the primary reason for imposing a disclosure obligation is to ensure public access to data showing that a treatment is *ineffective* for an off-label use. Therefore, many of the justifications for maintaining confidentiality of this information are inapplicable. While there may be some potential for harm in individual cases, a higher burden should be placed on the manufacturer to establish that such harm is actually likely to occur.<sup>142</sup> Finally, the public benefit from disclosure in the form of better medical treatment is substantial and should also be given significant weight in determining whether disclosure is appropriate.<sup>143</sup>

### B. Alternatives to Disclosure by Manufacturers

In light of even residual concern about competitive harm, it might be argued that an affirmative public disclosure requirement is not necessary. Instead, if adequate *production* of research into off-label uses is secured, it is only necessary to require that this information be reported to the FDA. If the information submitted suggests that action is appropriate, the FDA is capable of requiring additional warnings or labeling changes, or even withdrawing approval, if necessary.

There are, however, good reasons to believe that the public interest will not be adequately protected by FDA oversight of post-approval research data. Skepticism about reliance on FDA action alone is supported by the observation that, even in the high-profile case of the off-label prescription of SSRIs to minors, these drugs were on the market for over ten years before the FDA finally issued an acknowledgment of the allegations of increased propensity for suicide and pediatric ineffectiveness. Even then, it announced only that the matter required "additional data and analysis."<sup>144</sup>

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<sup>142</sup> See McGarity & Shapiro, *supra* note 114, at 885–86 (arguing that because evidence regarding competitive harm is largely in control of manufacturers, burden should be on them to justify profit protections like exclusivity periods).

<sup>143</sup> See Richard S. Fortunato, Note, *FDA Disclosure of Safety and Efficacy Data: The Scope of Section 301(j)*, 52 *FORDHAM L. REV.* 1280, 1298–99 (1984) (discussing public benefits in context of discretionary disclosure by FDA).

<sup>144</sup> Press Release, Ctr. for Drug Evaluation & Research, FDA, FDA Public Health Advisory: Reports of Suicidality in Pediatric Patients Being Treated with Antidepressant Medications for Major Depressive Disorder (MDD) (Oct. 27, 2003), <http://www.fda.gov/cder/drug/advisory/mdd.htm>. In October 2003, the FDA issued a letter to health professionals discussing concerns about the use of SSRIs in children but did not issue any specific

There are several explanations for the FDA's failure to take necessary actions in situations like these. First, the FDA has dedicated insufficient resources to the task of monitoring pharmaceuticals in the post-approval period.<sup>145</sup> The number of employees devoted to post-approval activities is a small fraction of that responsible for the pre-approval process, and these employees may lack the necessary expertise to make a proper assessment of the data that are submitted.<sup>146</sup> While applicants are now required to pay a considerable sum in order to submit an NDA,<sup>147</sup> this additional revenue is permitted to be spent only on the review of NDAs.<sup>148</sup> As a result of these proceeds, the FDA staff devoted to pre-approval review has grown significantly; consequently, the number of NDAs approved by the FDA each year has increased as well.<sup>149</sup> Of course, this growth trend has led to a corresponding increase in the amount of information that is submitted to the agency after approval. Though the initial period of market use, when a large number of people will be exposed to a novel agent, is a crucial time in which to assess the safety of a drug, no provision was made to expand the FDA divisions responsible for reviewing adverse event reports or other data submitted on these products.<sup>150</sup> Therefore, a preexisting lack of resources has been exacerbated by the success of recent attempts to accelerate the approval process.

Compounding the problems posed by the lack of resources devoted to post-approval surveillance is the difficulty of the task in

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recommendations for physicians or patients. *See id.* Prozac and Paxil were approved by the FDA for the treatment of depression in 1987 and 1992 respectively. *See* Diaz, *supra* note 12, at 87–88 (discussing Prozac); Press Release, Ctr. for Drug Evaluation & Research, FDA, Questions and Answers on Paxil (Paroxetine Hydrochloride) (June 19, 2003), <http://www.fda.gov/cder/drug/infopage/paxil/paxilQ&A.htm> (discussing Paxil).

<sup>145</sup> *See* Noah, *supra* note 50, at 452–53.

<sup>146</sup> *See id.* at 452 (noting that few FDA employees have advanced degrees in disciplines such as biostatistics or epidemiology).

<sup>147</sup> *See* Prescription Drug User Fee Act of 1992, 21 U.S.C. § 379h (2000) (designating fee of \$258,451 for NDA in fiscal year 2002).

<sup>148</sup> 21 U.S.C. § 379h(g)(1) (2000). This provision was included to satisfy manufacturers who had complained about the time required for NDA approval. *See* Noah, *supra* note 50, at 463–64 & n.62.

<sup>149</sup> *See* FDA, DEP'T OF HEALTH & HUMAN SERVS., MANAGING THE RISKS FROM MEDICAL PRODUCT USE: CREATING A RISK MANAGEMENT FRAMEWORK 17 (1999), available at <http://www.fda.gov/oc/tfrm/riskmanagement.pdf> (noting forty percent increase in number of approvals per year since introduction of user fee program); Merrill, *supra* note 22, at 1840 (describing success of user fee program in increasing numbers of staff and reducing review time for NDAs). *But see* Gardiner Harris, *F.D.A. Responds to Criticism with New Caution*, N.Y. TIMES, Aug. 6, 2005, at A1 (stating that time required for review of NDAs nearly doubled during first half of 2005).

<sup>150</sup> *See* Gerald A. Faich, Letter to the Editor, *Postmarketing Surveillance: Beyond MedWatch*, 270 JAMA 2180 (1993) (noting that “the proportion of manpower and funding allocated for postapproval work has actually declined”).

question. When submission of mere summaries or published reports is required, there exists greater potential that a manufacturer may have concealed information or analyzed the data in a way that puts the results in the best possible light. Under such circumstances, it may be particularly difficult to protect against data manipulation, or to see through the industry's "spin" placed on data submitted to the FDA.<sup>151</sup> When full reports from post-approval trials are submitted to the agency as part of an SNDA, delay can become an issue. FDA reconstruction of submitted data is responsible for much of the length of the original NDA process.<sup>152</sup> Because SNDAs are not given high priority for review,<sup>153</sup> it may take even longer for the FDA to review post-approval data, despite the greater urgency of determining the efficacy of a product that is already on the market and being prescribed for the condition for which supplemental approval is being sought. Ironically, the length of the review process may be inimical to public health, because it prolongs the period during which consumers are exposed to a potentially ineffective drug.

Even if there are questions about the FDA's ability to protect the public interest, one might argue that release of information through the FOIA is the appropriate method of addressing such suspicions. The purpose of the FOIA, after all, is to allow for public monitoring of agency decisionmaking. If the goal is simply to gain access to information for public use, the FOIA arguably already provides sufficient opportunity to obtain public access to exactly that information which the public interest demands.

Even disregarding the considerable uncertainty surrounding the applicability of the FOIA to clinical data,<sup>154</sup> there are several problems with this approach in the present context. First, reliance upon the FOIA would further delay the disclosure of this information. The FDA receives a large number of FOIA requests each year, and typically has a considerable backlog.<sup>155</sup> Furthermore, the submitter of the information has a right to challenge the agency's decision to

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<sup>151</sup> The main concern here might not be fabrication or misrepresentation of data, but rather legitimate data analyses that deemphasize or obscure issues that the FDA might otherwise discover if in possession of all data. Cf. *Pass Legislation to Force Disclosure of Drug Info*, CONSUMER REP., Mar. 2005, at 61 (noting that manufacturer's published study on Paxil referred to increased suicide risk as "mere emotional instability").

<sup>152</sup> See Merrill, *supra* note 22, at 1784–86 (describing labor-intensive and time-consuming data reconstruction process).

<sup>153</sup> See Weeks, *supra* note 42, at 663.

<sup>154</sup> See *supra* Part III.A.

<sup>155</sup> See Merrill, *supra* note 22, at 1785–86. Though there are limits on the amount of time allowed for responding to a FOIA request, these limits may be extended under certain circumstances. See 5 U.S.C. § 552(a)(6)(A), (6)(B)(i) (2000) (imposing twenty-day time limit with possibility for extension).

release it through a "reverse-FOIA" lawsuit under the Administrative Procedure Act.<sup>156</sup> Therefore, the public disclosure of information may be delayed pending the outcome of protracted litigation and subsequent appeals. Second, resources dedicated to handling FOIA requests necessarily subtract from those which can be devoted to the many other important functions of the FDA. Any public benefits derived from increased disclosure could be negated by decreased attention to new drug approval or postmarketing surveillance.

In addition, the importation of trade secret law into this regulatory setting may create problems of its own.<sup>157</sup> In a typical trade secret dispute, the opposing parties are members of a common industry, bringing to the case a great deal of the relevant knowledge about the value of the information in question.<sup>158</sup> However, in the regulatory setting, the agency is not particularly well-prepared to refute an industry member's arguments regarding the necessity for nondisclosure and thereby to make a well-informed determination on the consequences of the decision.<sup>159</sup> Faced with the prospect of opening a "Pandora's Box" by choosing disclosure,<sup>160</sup> the agency is likely to choose to err on the side of confidentiality. Should the agency decision be challenged in court, the requesting party, typically a consumer or consumer advocate group, is likely to face similar problems contesting the industry's claim of competitive harm.<sup>161</sup>

For these reasons, it seems more desirable for a solution to focus on disclosure by the manufacturer rather than the FDA. Placing the burden of disclosure directly on the manufacturer, enforced through FDA regulations, also has the advantage that the manufacturer will bear the consequences of noncompliance. Pharmaceutical manufacturers are already subject to FDA regulation in connection with many of their activities related to an approved drug. As a result, the FDA can exert considerable influence over manufacturers, who often comply with the agency's demands without much resistance.<sup>162</sup> A

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<sup>156</sup> See *Chrysler Corp. v. Brown*, 441 U.S. 281, 317-19 (1979) (providing for reverse-FOIA-type lawsuits brought by "adversely affected or aggrieved" parties seeking judicial review of agency decision to disclose information under Administrative Procedure Act § 10(a)).

<sup>157</sup> See Mary L. Lyndon, *Secrecy and Innovation in Tort Law and Regulation*, 23 N.M. L. REV. 1, 33-35 (1993) (discussing difficulties of application of trade secret law in other regulatory contexts).

<sup>158</sup> See *id.* at 35.

<sup>159</sup> See *id.* at 34-35.

<sup>160</sup> See *id.* at 33-34.

<sup>161</sup> See *id.* at 34-35 (noting that parties who are not market competitors will likely not have information to challenge industry claims of competitive harm).

<sup>162</sup> See Merrill, *supra* note 22, at 1781-82 ("[I]n the new drug approval process . . . [the] FDA exercises effectively unchallenged authority to dictate the number and kinds of

manufacturer's desire to avoid increased agency scrutiny, sanctions, delays, or even withdrawal of approval will likely create an important incentive to provide full and truthful disclosures in response to agency requests.

*C. A Starting Point for a Solution: The Best Pharmaceuticals for Children Act of 2002*

Given the inadequacies of the alternatives considered, a more thoroughgoing solution to the problem is necessary—one that addresses both production *and* disclosure of research that will inform the medical community and maximize the benefit to be gained from off-label treatments. One potential model for a solution might be found in recent legislative efforts addressing a specific class of off-label uses. Initiatives such as the Best Pharmaceuticals for Children Act of 2002 (BPCA) and its predecessors<sup>163</sup> provide incentives for drug manufacturers to test their products in pediatric populations in order to provide a basis for appropriate labeling information for physicians to consult when prescribing these drugs for children.<sup>164</sup> For many of the reasons discussed in this Note, pharmaceutical manufacturers have not historically sought formal labeling changes for approved products in order to provide proper instructions for pediatric use, even when such use was common.<sup>165</sup> Because there were no guidelines, physicians often inappropriately estimated dosage based on body size,<sup>166</sup> a practice that potentially placed children at risk of adverse effects and/or underdosing.<sup>167</sup> Children also may have been denied beneficial treatments because doctors were unwilling to pre-

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studies required to support approval . . ."); O'Reilly & Dalal, *supra* note 29, at 300–01 (mentioning drug companies' fear of "regulatory displeasure").

<sup>163</sup> Best Pharmaceuticals for Children Act (BPCA), 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.). The BPCA expanded and modified an existing pediatric exclusivity program that had been enacted as part of the FDAMA. See Lauren Hammer Breslow, Note, *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, 133 (2003).

<sup>164</sup> See Breslow, *supra* note 163, at 134.

<sup>165</sup> See *id.* at 133–34. In addition to the lack of reliable incentives to conduct research on off-label uses generally, see *supra* Part II.A, in the area of pediatric testing, additional disincentives are posed by the exploitative history of clinical research on children and the heightened fear of tort liability resulting from adverse effects during clinical testing. See Cooper, *supra* note 89, at 520 (discussing additional reasons why pediatric studies are not conducted); Breslow, *supra* note 163, at 135–44 (describing history of abuses and tort liability surrounding pediatric pharmaceutical testing).

<sup>166</sup> See Breslow, *supra* note 163, at 146–47.

<sup>167</sup> See David M. Smolin, *Nontherapeutic Research with Children: The Virtues and Vices of Legal Uncertainty*, 33 CUMB. L. REV. 621, 629 (2003).



scribe unapproved medications in light of uncertainty about the efficacy and risk for pediatric patients.<sup>168</sup>

The BPCA uses a “voluntary incentive structure” to promote research in pediatric populations.<sup>169</sup> After appropriate research targets are identified, the FDA contacts manufacturers and offers a six-month extension of market exclusivity (pediatric exclusivity) for a product if the manufacturer agrees to conduct specified research in pediatric subjects.<sup>170</sup> Since this extension can only be granted to a drug that presently enjoys market exclusivity under an existing patent or via some other means, pediatric exclusivity is ineffective in promoting pediatric research into drugs without ongoing market exclusivity.<sup>171</sup>

The BPCA, however, includes a mechanism by which pediatric labeling information might be produced for these drugs as well. Under the BPCA, drugs lacking market exclusivity, but for which pediatric labeling information would still be useful, are specifically identified.<sup>172</sup> If the manufacturer declines to conduct research after it has been asked to do so, the Department of Health and Human Services (DHHS) can seek third-party researchers to undertake such research, for which funding is provided.<sup>173</sup> This provision ensures that the production of pediatric labeling information does not depend on the cooperation of manufacturers.

The legislative schemes designed to address pediatric labeling help to illustrate some of the issues confronted in developing a solution to the gap in off-label research. Obviously, the first issue is to identify those off-label uses for which research is most needed. Under the FDAMA’s pediatric exclusivity provisions, the DHHS would consult with pediatric experts and construct a “Pediatric Priority List,” a list of candidate drugs for which pediatric labeling information is needed; the manufacturers of these drugs would be asked to conduct

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<sup>168</sup> See *id.*; Cooper, *supra* note 89, at 520.

<sup>169</sup> See Breslow, *supra* note 163, at 173–91 (criticizing use of voluntary incentive structure for this purpose).

<sup>170</sup> See 21 U.S.C. § 355a (2000); see also Breslow, *supra* note 163, at 154–73 (describing development of pediatric exclusivity under FDAMA and BPCA).

<sup>171</sup> The six months of exclusivity will begin following the expiration of a patent or other market exclusivity period, such as the five years of market exclusivity for “new molecular entit[ies]” under Hatch-Waxman, or the seven years of marketing exclusivity for drugs used to treat rare diseases under the Orphan Drug Act. See Cooper, *supra* note 89, at 522–23.

<sup>172</sup> See *id.* at 530.

<sup>173</sup> See *id.* at 526–27, 530–31. It has been suggested, perhaps unrealistically, that manufacturers will undertake these studies voluntarily in order to avoid the negative publicity resulting from a refusal to undertake research important for the safety of children. See *id.* at 527.

trials designed to yield this information. While the Pediatric Priority List has been abandoned under the BPCA,<sup>174</sup> something of this sort could be useful for identifying appropriate targets for off-label research more generally. One challenge will be selecting off-label uses that are sufficiently widespread and promising to warrant research efforts and resources. This task might also require the development of better methods for tracking off-label use in the field, perhaps through voluntary or mandatory reporting at the physician or pharmacist level.

The questions of whether pediatric research should be mandatory and whether it should be incentivized through market exclusivity have generated some disagreement. Prior to enactment of the BPCA, as the FDAMA pediatric exclusivity provisions were coming up for renewal, the FDA and the DHHS suggested that the obligation to produce pediatric research should not be voluntary. Instead, they proposed that the FDA should have the authority to *require* pediatric research, backed up by civil penalties and sanctions.<sup>175</sup> These suggestions, however, were not ultimately incorporated into the BPCA.<sup>176</sup>

Along similar lines, commentators have gone further and proposed that grants of market exclusivity should not be used to secure manufacturers' compliance, noting that even a short period of market exclusivity can reap huge profits for a successful drug.<sup>177</sup> For example, while even the pharmaceutical industry's highest estimates place the cost of requested pediatric trials at between five million and thirty-five million dollars, six months of market exclusivity for many drugs can yield hundreds of millions of dollars in additional profits.<sup>178</sup> To those who believe that studies like these are properly considered the manufacturer's duty, such profits seem like an unjustified windfall.<sup>179</sup> Likewise, critics argue that the BPCA's provision for government funding of pediatric research when manufacturers decline to undertake these

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<sup>174</sup> The FDA recommended elimination of the list because its costs exceeded its value in identifying appropriate targets and because some manufacturers erroneously believed that only drugs on the list were eligible for exclusivity under the program. *See id.* at 521, 529. These reasons seem to indicate that the priority list is potentially useful, but was not implemented effectively under the FDAMA.

<sup>175</sup> *See id.* at 525–26.

<sup>176</sup> *See id.* at 527.

<sup>177</sup> *See* Breslow, *supra* note 163, at 167–70.

<sup>178</sup> *See id.* at 167–68 (pointing out that pediatric studies for Prilosec cost between two and four million dollars, while manufacturer earned 1.4 billion dollars from extended period of market exclusivity).

<sup>179</sup> *See id.* at 167–70.

studies themselves unfairly places the cost upon taxpayers instead of drug companies.<sup>180</sup>

As part of an expanded program to investigate off-label uses generally, direct government funding for third parties to conduct research when manufacturers decline to do so would probably be prohibitively expensive. Ideally, however, the viability of the solution should not depend upon whether a product happens to possess unexpired market exclusivity at the time an off-label use emerges. More generally, the production of useful research should not depend solely upon the manufacturer's incentives and disincentives.

In order to address the problem more completely without such arbitrariness, a mandatory obligation to conduct research into off-label uses should be recognized. At the same time, compensatory options besides market exclusivity ought to be considered. Another possibility might be to offer compensation on a sliding scale, in which the reward offered is inversely related to the profits derived from the product.<sup>181</sup> Even if costs imposed on manufacturers by a mandatory research obligation are ultimately passed onto consumers, the net cost is likely to be less than that resulting from a longer period of monopoly profits.<sup>182</sup>

Finally, the BPCA does not adequately address the necessity for disclosure of the results of research undertaken under its provisions. The award of exclusivity is contingent upon the completion of studies satisfying the terms of the FDA's written request, regardless of whether or not this information ultimately leads to changes in product labeling.<sup>183</sup> Thus, far from providing for effective publication of this information, the BPCA does not even require that it be made part of the labeling information. Indeed, the FDA has apparently encountered resistance from manufacturers asked to make labeling changes reflecting unfavorable research findings.<sup>184</sup> While the BPCA does provide that data from research conducted by third parties after manufacturers' refusals are considered to be in the public domain and will

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<sup>180</sup> See *id.* at 189 (arguing that consumers are forced to pay costs of research, whether through direct funding of research or through cost of granting market exclusivity).

<sup>181</sup> During the drafting of the BPCA a proposal was made to make pediatric exclusivity unavailable for "blockbuster drugs" (drugs earning over \$800 million in sales during the exclusivity period). See *id.* at 169.

<sup>182</sup> See *id.* at 189.

<sup>183</sup> See Cooper, *supra* note 89, at 522.

<sup>184</sup> See Breslow, *supra* note 163, at 171 ("[T]he FDA reported great difficulty in convincing drug manufacturers to list unfavorable pediatric research results on their drug labels.") (internal quotation omitted); Harris, *supra* note 149, at A1 (noting fourteen-month negotiation between FDA and Merck before heart attack risks were added to Vioxx labeling).

be available for comment and dissemination,<sup>185</sup> this category comprises only a fraction of the research conducted under the BPCA scheme.

Since, as noted above, a program addressing off-label use probably could not rely upon publicly funded third-party research, another approach to ensure dissemination would be necessary. Where labeling changes are appropriate, the FDA must have the authority and willingness to demand such changes. In addition, research produced by manufacturers as part of a general off-label research program should not be considered proprietary information. Like data produced by third parties under the BPCA, the results of research conducted by manufacturers should be publicly accessible. Efforts should also be made to publish this research in the medical literature, where it is most likely to be found by physicians seeking studies of off-label uses to inform their practices.<sup>186</sup> To allay concerns about the reliability of industry-produced or industry-funded studies, the FDA might participate in the analysis of the data and work in conjunction with industry researchers to shape the ultimate form of this publication. Any information that would be appropriate for nondisclosure due to its confidential commercial character could be withheld from the final publication. However, studies should be designed to minimize this possibility, and the manufacturer's mere assertions of competitive harm should not be sufficient to prevent publication.<sup>187</sup>

### CONCLUSION

A drug's effectiveness for an unapproved use usually will not have been established to the level of certainty required for FDA approval. In many cases no formal clinical trials investigating the use will have been performed. The agency's hands-off approach with respect to off-label uses is strikingly inconsistent with its general role as a gatekeeper for pharmaceutical products, ensuring that all pharmaceuticals meet high standards for safety and effectiveness before reaching the public. In the case of an off-label use, the gatekeeping role is left to the prescribing physician, who may lack the ability or inclination to rely upon proper information. In the absence

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<sup>185</sup> See Cooper, *supra* note 89, at 531–32.

<sup>186</sup> See Breslow, *supra* note 163, at 184 (noting argument that pediatricians are unlikely to consult *Federal Register* for guidance in treatment decisions).

<sup>187</sup> While courts often recite the rule that “[c]onclusory and generalized allegations” are insufficient to establish competitive injury for purposes of Exemption 4 of the FOIA, see *Pub. Citizen Health Research Group v. FDA*, 704 F.2d 1280, 1291 (D.C. Cir. 1983), the outcomes of these cases suggest that manufacturers' claims should be scrutinized more closely. See *supra* notes 106–08 and accompanying text.

of relevant, published research findings, decisions to prescribe drugs for off-label uses will be guided by less reliable sources of knowledge. This result is contrary to the goals of evidence-based medicine.

Unfortunately, strong incentives do not currently exist for manufacturers to pursue research into the safety and effectiveness of off-label uses of their products. Even if the necessary research were conducted, there are no guarantees that the resulting data would be made available to prescribing physicians. Existing avenues for disclosure have been frustrated by manufacturers' proprietary claims over their research data and its characterization as confidential commercial information. The claim that significant competitive harm would result from the release of this type of research, however, seems dubious. The pediatric exclusivity scheme embodied in the BPCA addresses, to a limited degree, the production of research into a particular type of off-label use, but does not provide for effective disclosure of the results of this research. A more desirable solution, addressing off-label uses more generally, could take the BPCA as a starting point and add to it an enforceable obligation on manufacturers to conduct research into beneficial off-label uses and to make the results public in a useful form.