

**BIG DATA AND PHARMACOVIGILANCE: USING HEALTH INFORMATION
EXCHANGES TO REVOLUTIONIZE DRUG SAFETY**

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ABSTRACT

Data on individual patients collected through state and federal health information exchanges has the potential to usher in a new era of drug regulation. These exchanges, produced by recent health care reform legislation, will amass an unprecedented amount of clinical information on drug usage, demographic variables, and patient outcomes. This information could aid the Food and Drug Administration (“FDA”) with post-market drug surveillance because it more accurately reflects clinical practice outcomes than the trials the FDA relies upon for drug approval. However, even with this data available, the market-driven impetus to use it to police drugs is weak. This is fixable; the post-market drug regulatory process needs new incentives to boost third party participation. While a

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variety of mechanisms could achieve this, the best option for generating robust results may be an administrative bounty proceeding that will allow third parties to submit evidence to the FDA to contest the claimed safety and efficacy profiles of drugs already on the market. This Article uses a case study of Merck's former blockbuster drug Vioxx to demonstrate how this system might work. In creating a new incentive that counters the powerful financial motivation of drug manufacturers to obscure or misrepresent safety profiles, the proposed bounty proceeding could lead to an improved balance of the risks and benefits of drugs used by the American public. More broadly, this Article illustrates how to create an incentive for the private sector to supplement regulatory activity in a complex field.

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I. INTRODUCTION

Every day 2.5 quintillion bytes of data are created—so much that 90 percent of the world’s data has been produced in the last two years alone.¹ This information revolution is transforming education, labor markets, and social relationships, and is creating entirely new industries.² Some of the greatest advances have and will come in biotechnology and bioinformatics, where “big data” is altering new drug development, clinical practices, and health care financing.³ It also has the potential to lead to a new kind of understanding of how drugs work in the real world. In 1991, the Food and Drug Administration (“FDA”) based its approval of the cholesterol-lowering drug simvastatin on pre-market controlled clinical studies that included a total of 2423 patients.⁴ In 2011 alone, health care providers, just in the United States, wrote almost a hundred *million* prescriptions for the drug.⁵ Imagine the impact of being able to analyze data from every one of those patients to evaluate whether simvastatin is safe and effective. Better yet, imagine analyzing data from every patient who has ever taken the drug in every country in the world. That is the vision of a drug regulatory system powered by big data. Historically, that type of research has been unachievable. But now, for the first time in human

¹ *Bringing Big Data to the Enterprise*, IBM, <http://www-01.ibm.com/software/ph/data/bigdata/> (last visited Aug. 23, 2013).

² Peter F. Drucker, *Beyond the Information Revolution*, ATLANTIC (Oct. 1, 1999, 12:00 PM), <http://www.theatlantic.com/magazine/archive/1999/10/beyond-the-information-revolution/304658/>.

³ See Ryan Abbott, *Overcoming Barriers to a Global Treaty on Medical Funding and R&D*, 7 REVISTA ELETRÔNICA DO IBPI [J. BRAZILIAN INST. FOR INTELL. PROP.] 70 (2012) (Braz.).

⁴ MERCK SHARP & DOHME LTD., MERCK & CO., INC., HIGHLIGHTS OF PRESCRIBING INFORMATION: ZOCOR (SIMVASTATIN) TABLETS 7 (2010), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019766s078lbl.pdf.

⁵ IMS INST. FOR HEALTHCARE INFORMATICS, THE USE OF MEDICINES IN THE UNITED STATES: REVIEW OF 2011, at 38 (2012), *available at* http://www.imshealth.com/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/IHII_Medicines_in_U.S_Report_2011.pdf.

history, it is a possibility.

However, it remains just that—a possibility. Although a vision for a new type of post-market regulatory system exists, a plan does not. If the vision is to come to fruition, policymakers must address some operational challenges. First, the right kinds of data will need to be collected. Second, researchers have to aggregate the raw data in order to analyze it more easily. Third, the aggregated data will need to be effectively plugged into the regulatory process. Unfortunately, because an industry motivated by profit rather than patient outcomes dominates our current post-market drug regulatory system, it is not structured to meaningfully use such data. While another stakeholder in the process—the FDA—has a different set of motivations and political pressures, the agency lacks the resources, information, and entrepreneurial drive of the 1.1 trillion-dollar-a-year private industry it oversees.⁶ Third parties such as insurance companies, academics, and rival firms have some role, but their incentives to police the drug market are relatively weak despite the potential public health benefits. Maximizing the data’s value requires restructuring market participant incentives to enhance third party engagement in post-market surveillance. There are a number of ways to accomplish this, and the ideal solution may be a mix that offers a variety of incentives. However, this Article argues that the single most effective mechanism may be a new administrative bounty proceeding modeled after the False Claims Act qui tam regime.⁷

⁶ *Global Drug Sales to Top \$1 Trillion in 2014: IMS*, MONEYCONTROL.COM (Apr. 20, 2010, 2:29 PM), http://www.moneycontrol.com/news/business/global-drug-sales-to-top-361-trillion2014-ims_452580.html. By contrast, “Congress has starved the agency of funds, even as the FDA’s functions have expanded vastly.” Lawrence O. Gostin, *The Deregulatory Effects of Preempting Tort Litigation: FDA Regulation of Medical Devices*, 299 JAMA 2313, 2314 (2008).

⁷ The term “qui tam” is an abbreviation of a Latin phrase that means: “he who brings a case on behalf of our lord the King, as well as for himself.” FALSE CLAIMS ACT CASES: GOVERNMENT INTERVENTION IN QUI TAM (WHISTLEBLOWER) SUITS, U.S. DEP’T OF JUSTICE (internal quotation

This proposal is not intended to be anti-industry. Pharmaceutical manufacturers provide a critical societal good through their role in drug development, approval, and commercialization. The vast majority of approved drugs have the potential to benefit patients. Even for those that do not, sponsors may legitimately believe that their products are safe and effective when they are approved, and evidence to the contrary may not emerge until a drug's use is widespread.⁸ However, it is inevitable that unsafe and ineffective drugs will obtain FDA approval because no pre-market regulatory system can work perfectly.⁹

Part I.A examines current drug regulation processes and shortcomings, and finds that the FDA continues to rely on the same painfully limited resources it has depended on for the past

marks omitted), *available at* <http://www.justice.gov/usao/pae/Documents/fcaprocess2.pdf> (last visited Aug. 23, 2012). It is a legal device that permits a private entity to sue another for violating a government regulation, when there is a statute that provides for a penalty. *See id.* Suits are brought for the government as well as the plaintiff. *Id.*

⁸ Throughout this Article, “unsafe” refers to products or practices with unfavorable risk/benefit profiles. All drugs have the potential to produce adverse reactions, and by definition most prescription drugs are “not safe for use except under the supervision of a practitioner licensed by law to administer such drug.” 21 U.S.C. § 353(b)(1)(A) (2006).

⁹ The problem of unsafe and ineffective drugs is significant. With regards to drug safety, “[i]t has been estimated that as many as half of all new drugs have at least one serious adverse effect that is unknown at the time of drug approval.” BENGT D. FURBERG & CURT D. FURBERG, *EVALUATING CLINICAL RESEARCH: ALL THAT GLITTERS IS NOT GOLD* 8 (2d ed. 2007). About 4% of FDA-approved drugs are later withdrawn from the market for safety reasons. Mei Sheng Duh et al., *The Role of Epidemiology in Drug Safety Litigations*, FOOD & DRUG L. INST. UPDATE, Nov.–Dec. 2007, at 31, 31. With regards to efficacy, it has been estimated that 30% to 60% of prescriptions fail to produce their expected pharmacological action. Barbara J. Evans, *Seven Pillars of a New Evidentiary Paradigm: The Food, Drug, and Cosmetic Act Enters the Genomic Era*, 85 NOTRE DAME L. REV. 419, 498 (2010). Although the use of ineffective medicines may not cause direct injuries, it wastes resources and undermines trust in medicine. Vinay Prasad et al., *A Decade of Reversal: An Analysis of 146 Contradicted Medical Practices*, 88 MAYO CLINIC PROC. 790, 790 (2013). It may also cause “lost-chance” injuries, as an alternative treatment might have been effective. *See* Ryan Abbott & Michael Cohen, *Medico-Legal Issues in Cardiology*, 21 CARDIOLOGY REV. 222, 222 (2013) (discussing the “loss of chance” doctrine in the malpractice context).

fifty years.¹⁰ Namely, the FDA relies on industry-sponsored clinical trials that only require a drug's sponsor to show that the drug produces a slight improvement over a placebo in a highly selective group of research volunteers. While these pre-market trials are an indispensable part of the drug regulatory scheme, there are serious limitations with extrapolating results to the more diverse, general population. Beyond this, the FDA has struggled to effectively evaluate approved drugs because its regulatory model is profoundly unbalanced. Merck's former blockbuster pain medication Vioxx, which was withdrawn from the market after causing a large number of patient deaths, well illustrates the problems with the current system.

Part I.B argues that recent health care reform initiatives are creating the primary resource for a pharmacovigilance system powered by big data. Through these recent reform initiatives, the federal government is promoting widespread use of health information technology ("HIT")¹¹ and health information exchange ("HIE"),¹² particularly through the creation of national and state-based health information exchanges.¹³ HIEs, not to be mistaken in this Article with the more

¹⁰ The FDA has been able to require drug sponsors to conduct pre-market randomized controlled clinical trials to prove that a candidate drug is safe and effective as a condition for market approval since 1962. Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962).

¹¹ HIT involves the electronic exchange of health information. For example, it can include the use of electronic medical records ("EMR"s) instead of paper medical records, the electronic storage and transmission of clinical lab results or radiographic images, the use of electronic prescribing instead of traditional hand-written prescriptions, and clinical decision support systems to help providers by recommending best practices. BARRY R. FURROW ET AL., *HEALTH LAW: CASES, MATERIALS AND PROBLEMS* 38 (6th ed. 2008).

¹² HIE refers to the ability to transfer real-time health information.

¹³ The Health Information Technology for Economic and Clinical Health Act ("HITECH Act") established state and federal HIEs to facilitate the exchange of real-time health information between providers. American Recovery and Reinvestment Act of 2009, Pub. L. No. 111-5, § 13101, 123 Stat. 115, 228-42. The vision underlying HIEs is that a patient might be seen one day at Stanford University Hospital in Palo Alto and the next day at Kaiser Permanente Los Angeles Medical Center, but that providers at both organizations would have real time access to the entirety of the patient's medical notes, laboratory results, and radiologic imaging through a centralized database.

prominently discussed health *insurance* exchanges,¹⁴ will generate a never-before-seen amount of clinical data. Although health care providers collect this data principally for use in direct patient care, this data has a number of secondary applications in areas such as drug regulation. However, while HIEs can theoretically be used for regulation under the existing frameworks, this is far from certain to occur. A number of problems need resolution before execution can be successful. For example, concerns have been raised regarding HIEs' interoperability, reporting standards and requirements, and sustainability. Use of HIEs for pharmacovigilance raises critical patient privacy issues, but that use is permitted under federal laws governing the confidentiality of health information.¹⁵ Ultimately, while the risk of privacy loss can never be eliminated, it can be significantly minimized through effective security protocols and the threat of civil and criminal liability.

Part II argues that to achieve meaningful use of information from HIEs, policymakers should restructure the regulatory process to motivate third parties to play a more active role by creating new incentives that counter the profit-oriented motivation of industry. If there are effective advocates for both consumers and industry in the post-approval regulatory system, the process will be balanced in a way that will ultimately benefit patients. A restructured regulatory process that creates an administrative bounty proceeding to incentivize third parties to submit data on drug safety and efficacy to the FDA would improve public health. Although some third

¹⁴ Health *insurance* exchanges are State agencies or State-established non-profits created by the Affordable Care Act ("ACA") to assist qualified individuals and employers to enroll in qualified health plans. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 1311(b)–(d), 124 Stat. 119, 173–78 (2010) (codified as 42 U.S.C. § 18031(b)–(d)).

¹⁵ KRISTEN ROSATIV ET AL., EHEALTH INITIATIVE FOUND., AN ANALYSIS OF LEGAL ISSUES RELATED TO THE USE OF ELECTRONIC HEALTH INFORMATION IN PHARMACOVIGILANCE PROGRAMS 2–8 (2008), *available at* <http://www.brookings.edu/~media/events/2008/6/13-drug-safety/rosati--ehi-drug-safety-collaboration-legal-guidance-developed-by-coppersmith-gordon-04-15-08>.

parties would submit data even without this new mechanism, a monetary incentive is necessary to achieve vigorous participation.

Then there is the financing question: Where will the money for these bounties come from? One option is for the pharmaceutical industry to bear the cost. Passing the costs of administrative bounty proceedings onto the pharmaceutical industry would create an even stronger incentive for companies to actively self-police their own products. On the other hand, despite record revenue and high profit margins, the pharmaceutical industry claims that the cost of drug approval is unsustainable and that existing regulations stifle innovation. Ultimately, the most efficient cost bearer for the financial prizes may be the country's largest health care insurer, provider, and financier—the federal government.¹⁶ After all, no party stands to gain more under this system than the government.¹⁷

Petitioner rewards, paid by the government, could be structured under a strict liability system to reflect a portion of the money that the federal government will save by avoiding adverse effects and medically ineffective therapies in patients with government health insurance. In the event a pharmaceutical company is found to have negligently misrepresented a drug's risk–benefit profile, the company could be directly responsible for the cost of awards based on a portion of a drug's revenue. If product sponsors are found to have acted willfully, recklessly, or with gross negligence, they could be responsible for treble damages.

¹⁶ Through the Veteran's Administration, the U.S government is the largest direct health care provider in the country. *About VHA*, U.S. DEP'T VETERANS AFFAIRS, <http://www.va.gov/health/aboutVHA.asp> (last updated Aug. 7, 2013). Federal, state, and local governments together directly purchase as much as 45% of all health care services. FURROW ET AL., *supra* note 11, at 638.

¹⁷ The federal government, at least in the aggregate, bears the highest financial cost of drug safety problems. For individual patients, however, ineffective and unsafe medicines may cause serious side effects or even death.

This proposal is in accord with longstanding trends in regulatory governance that favor incentives and voluntary compliance over direct compulsion models.¹⁸ Relatively flexible, incentive-based regimes that rely on market mechanisms are increasingly replacing command-and-control schemes with detailed, mandatory requirements.¹⁹ This permits greater reliance on self-regulation and greater design flexibility for stakeholders and federal agencies.²⁰ An emphasis on incentive use and flexible regimes is incorporated in the Executive Order that governs federal regulatory initiatives.²¹ Financial incentives, in particular, have come to represent a critical regulatory instrument.²²

A. *POST-MARKET REGULATION OF DRUGS AND MEDICAL DEVICES*

1. *DRUG REGULATION AND POST-MARKET ASSESSMENT*

The FDA is the federal agency that ensures that products including pharmaceutical drugs,

¹⁸ Gillian E. Metzger, *To Tax, to Spend, to Regulate*, 126 HARV. L. REV. 83, 106 (2012).

¹⁹ Jon D. Hanson & Kyle D. Logue, *The Costs of Cigarettes: The Economic Case for Ex Post Incentive-Based Regulation*, 107 YALE L.J. 1163, 1174 (1998); see Eric W. Orts, *Reflexive Environmental Law*, 89 NW. U. L. REV. 1227, 1235–52 (1995). Hybrid models incorporating both market-based incentives and command-and-control regulation exist, for example in environmental regulation with tradable emissions. See Richard B. Stewart, *A New Generation of Environmental Regulation?*, 29 CAP. U. L. REV. 21, 21–26 (2001).

²⁰ See Orly Lobel, *The Renew Deal: The Fall of Regulation and the Rise of Governance in Contemporary Legal Thought*, 89 MINN. L. REV. 342, 371–404 (2004).

²¹ See Exec. Order No. 12,866 § 1(b)(3), (8), 3 C.F.R. 638, 639 (1994), *reprinted as amended in* 5 U.S.C. § 601 app. at 88–92 (2012); see also Exec. Order No. 13,563 § 4, 3 C.F.R. 215, 216 (2012), *reprinted as amended in* 5 U.S.C. § 601 app. at 102–03.

²² See Rena I. Steinzor, *Reinventing Environmental Regulation: The Dangerous Journey from Command to Self-Control*, 22 HARV. ENVTL. L. REV. 103, 115–17 (1998). There is a trend toward greater use of money as a regulatory tool; federal grants to states and localities increased from \$7 billion to \$96 billion from 1960 to 1985. *Garcia v. San Antonio Metro. Transit Auth.*, 469 U.S. 528, 552 (1985). The government is widely privatizing services and programs with the hope that they will improve through profit incentives. See Michael J. Trebilcock & Edward M. Iacobucci, *Privatization and Accountability*, 116 HARV. L. REV. 1422, 1451–53 (2003).

biological products, and medical devices are safe, effective, and secure.²³ In the case of prescription drugs, regulation can be roughly divided into a pre-market and a post-market assessment.²⁴ A pre-market assessment evaluates whether a drug is safe and effective before the product sponsor can place it on the market.²⁵ This requires product sponsors to test their candidate in various ways: initially there are laboratory and animal tests, and then, if early test data is promising, there are human population tests. Product sponsors have to submit a new drug application (“NDA”) to the FDA, which must include “full reports of investigations,” a list of the drug’s components, any proposed labeling, as well as “a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing.”²⁶ Approval is contingent on whether the FDA finds that the drug has a favorable risk–benefit profile.²⁷ Only 5 out of every 5000 experimental compounds will reach clinical trials, and the FDA will approve only one of those.²⁸ The FDA also ensures that drugs are appropriately labeled and marketed.²⁹

²³ The system proposed in this Article could apply equally well to any category of product the FDA regulates for which HIEs include use information. The FDA regulates a broad range of products including human drugs, vaccines, blood products, medical devices, cosmetics, veterinary products, tobacco products, dietary supplements, and foods. *FDA Fundamentals*, FDA, <http://www.fda.gov/aboutfda/transparency/basics/ucm192695.htm> (last updated May 6, 2013).

²⁴ The Food, Drug, and Cosmetic Act (“FDCA”) defines drugs in part as “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease” and “articles (other than food) intended to affect the structure or any function of the body of man or other animals.” 21 U.S.C. § 321(g)(1) (2006). Biological products are included in this definition, but are manufactured as a result of biological rather than chemical processes. *Drugs@FDA: Glossary of Terms*, FDA, <http://www.fda.gov/Drugs/informationondrugs/ucm079436.htm#D> (last updated Feb. 2, 2012).

²⁵ 21 U.S.C. § 355(a).

²⁶ 21 U.S.C. § 355(b)(1).

²⁷ New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452-01, 7470 (Feb. 22, 1985) (codified in scattered sections of 21 C.F.R.).

²⁸ *Intellectual Property*, PHRMA, <http://www.phrma.org/innovation/intellectual-property> (last visited Aug. 26, 2013).

²⁹ See 21 U.S.C. § 321(n); *id.* § 331(a), (b), & (k) (2006 & Supp. V 2011); *id.* § 321(m) (2006)

FDA oversight continues after a drug receives market approval. The Food, Drug, and Cosmetic Act (“FDCA”)³⁰ and the FDA’s regulations require the pharmaceutical industry to perform ongoing risk evaluation and mitigation.³¹ Product sponsors must keep records and report “clinical experiences” that may suggest a drug is unsafe or ineffective for its approved conditions of use.³² Product sponsors must also report certain adverse effects to the FDA.³³ In addition, they must submit annual reports “within 60 days of the anniversary date of U.S. approval of the application”³⁴ that include “information . . . that might affect the safety, effectiveness, or labeling of the drug product” as well as the “actions [that] the applicant has taken or intends to take as a result of this new information.”³⁵ The FDA and the Secretary of the Department of Health and Human Services (“HHS”) review drug safety profiles on an ongoing basis, and use this information to determine whether approved drugs should be withdrawn from the market.³⁶ The FDA may also require product sponsors to conduct or fund post-market clinical or observational

(labeling is an expansive concept that includes “all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article”); 21 C.F.R. § 201.100(d) (2006) (“[W]hether or not it is on or within a package from which the drug is to be dispensed, distributed by or on behalf of the manufacturer, packer, or distributor of the drug . . .”).

³⁰ For an explanation of the FDCA, see 25 AM. JUR. 2D *Drugs and Controlled Substances* § 100 (2004 & Supp. 2013).

³¹ CTR. FOR DRUG EVALUATION & RESEARCH & CTR. FOR BIOLOGICS EVALUATION & RESEARCH, FDA, U.S. DEP’T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: FORMAT AND CONTENT OF PROPOSED RISK EVALUATION AND MITIGATION STRATEGIES (REMS), REMS ASSESSMENTS, AND PROPOSED REMS MODIFICATIONS (2009), *available at* <http://www.fda.gov/downloads/Drugs/Guidances/UCM184128.pdf>.

³² 21 U.S.C. § 355(k).

³³ See 21 C.F.R. § 314.80(a) & (c) (2009) (defining “adverse drug experience” as “[a]ny adverse event associated with the use of a drug in humans”).

³⁴ 21 C.F.R. § 314.81(b)(2).

³⁵ *Id.* § 314.81(b)(2)(i).

³⁶ See 21 U.S.C. § 355(d)–(e).

trials in some circumstances.³⁷ Also, product sponsors must revise drug labels so that they “include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug.”³⁸

This post-market assessment process is vital because it is impossible to identify every safety concern in clinical trials and the number of patients exposed to a drug substantially increases after it is approved for sale.³⁹ Moreover, the general patient population is different from clinical study populations because patients in the general population are more likely to have secondary medical conditions and to be taking other medicines at the same time.⁴⁰ Both of these factors can affect how patients react to drugs.

2. *RANDOMIZED CONTROL TRIALS VERSUS OBSERVATIONAL STUDIES*

The FDA primarily relies on randomized controlled trials (“RCT”s) for its pre-market risk assessment. A RCT is a particular type of scientific experiment;⁴¹ its key feature is that study participants are assigned by chance to receive either the therapy being evaluated or another treatment. Although RCT design can be complicated, a basic RCT has two groups: an

³⁷ See INST. OF MED. OF THE NAT’L ACADS., *THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC* 17 (2007), available at http://books.nap.edu/openbook.php?record_id=11750&page=R1.

³⁸ 21 C.F.R. § 201.57(c)(6)(i).

³⁹ CTR. FOR DRUG EVALUATION & RESEARCH & CTR. FOR BIOLOGICS EVALUATION & RESEARCH, FDA, U.S. DEP’T OF HEALTH & HUMAN SERVS., *GUIDANCE FOR INDUSTRY: GOOD PHARMACOVIGILANCE PRACTICES AND PHARMACOEPIDEMIOLOGIC ASSESSMENT* 3 (2005) [hereinafter *GUIDANCE FOR INDUSTRY*], available at <http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126834.pdf>.

⁴⁰ *Id.*

⁴¹ RCTs are a subtype of prospective studies. Prospective studies watch for outcomes, such as the development of a disease, during a study period and relate this to other factors, while retrospective studies look backwards and examine variables in relation to an established outcome. Most clinical trials are prospective studies, as they have fewer potential sources of bias and confounding. For an example of RCT structure, see Ryan B. Abbott et al., *A Randomized Controlled Trial of Tai Chi for Tension Headaches*, 4 EVIDENCE BASED COMPLEMENTARY & ALTERNATIVE MED. 107 (2007).

intervention group and a control group. In a new drug trial, patients who are assigned to the intervention group by what is essentially a sophisticated coin-flip, receive the investigational drug, while patients in the control group receive a placebo, which is a medically inert treatment such as a sugar pill. Alternatively, instead of an inert treatment, the control group may receive a comparator drug, which is a different medicine that is already approved for the studied indication and is used like a placebo as a reference.⁴² With either control group type, researchers can compare the results between groups to determine whether a statistically significant change has occurred. RCTs can be either a “blinded study”—when either the patients *or* the researchers are unaware of participants’ group assignment—or a “double-blinded study”—when *both* the patients and the researchers are unaware of the group assignments.

RCTs offer powerful benefits over non-randomized trials to the extent that RCTs (particularly double-blind, randomized, placebo-controlled trials) are the gold standard to evaluate an investigational new drug’s safety and efficacy.⁴³ No other study design so thoroughly eliminates selection bias and reduces the risk of confounding variables.⁴⁴ RCTs allow attribution of patient outcomes to the treatment patients receive rather than to other features of the patient population that might result in clinically favorable outcomes.⁴⁵ For this reason, in evidence-based medicine,⁴⁶ RCT results are considered “more definitive than any other type of clinical research

⁴² See, e.g., trials described in *infra* note 204. Also, some trials use no treatment controls, although this practice is usually reserved for the study of non-drug therapies when it is impossible to blind patients to their group assignment.

⁴³ Louise E. Parker et al., *Balancing Health Care Evidence and Art to Meet Clinical Needs: Policymakers’ Perspectives*, 15 J. EVALUATION CLINICAL PRAC. 970 (2009).

⁴⁴ See Bonnie J. Kaplan et al., *Evaluating Treatments in Health Care: The Instability of a One-Legged Stool*, 11 BMC MED. RES. METHODOLOGY 65 (2011).

⁴⁵ Ben A. Williams, *Perils of Evidence-Based Medicine*, 53 PERSP. BIOLOGY & MED. 106, 109 (2010).

⁴⁶ Evidence-based medicine (“EBM”) focuses on making health care decisions based on high-

information.”⁴⁷

Yet RCTs also have significant shortcomings—particularly with regards to detecting adverse events. RCTs are very resource intensive, which renders them expensive. The average cost of a single RCT for drug approval is \$15 million,⁴⁸ while the larger, multi-center RCTs can cost more than \$100 million.⁴⁹ Largely because clinical trials have such high costs, the Pharmaceutical Research and Manufacturers Association of America (“PhRMA”)⁵⁰ claims that a single drug approval costs, on average, more than \$1.2 billion (a controversial and disputed figure).⁵¹ Furthermore, because RCTs are so resource intensive, they tend to have small study sizes, which makes it difficult to detect problems that may be serious or life threatening but which rarely occur. The FDA noted that RCTs are impractical when the rates of concern are less common than 1:2000–3000.⁵² RCTs tend to be relatively short in duration (which makes it difficult to detect adverse effects that take a longer time to occur), and, additionally, they often make use of strict inclusion and exclusion criteria to limit confounding variables. For example, a

quality empirical research, evidence, and results. For a brief overview of EBM, see Romana Hasnain-Wynia, *Is Evidence-Based Medicine Patient-Centered and Is Patient-Centered Care Evidence-Based?*, 41 HEALTH SERVICES RES. 1 (2006).

⁴⁷ Kenneth Stanley, *Design of Randomized Controlled Trials*, 115 CIRCULATION 1164, 1164 (2007).

⁴⁸ Kaplan et al., *supra* note 44.

⁴⁹ Matthew Herper, *The Truly Staggering Cost of Inventing New Drugs*, FORBES.COM (Feb. 10, 2012, 7:41 AM), <http://www.forbes.com/sites/matthewherper/2012/02/10/the-truly-staggering-cost-of-inventing-new-drugs>.

⁵⁰ PhRMA is an organization composed of the country’s leading pharmaceutical industry R&D and biotech companies. *About PhRMA*, PHRMA, <http://www.phrma.org/about> (last visited Aug. 26, 2013). PhRMA claims that only two out of every ten approved medicines eventually recoups the money spent on its development. *Intellectual Property*, *supra* note 28.

⁵¹ Some independent experts have argued that the true cost of drug approval is far less. *See, e.g.*, Donald W. Light & Joel R. Lexchin, *Pharmaceutical Research and Development: What Do We Get For All That Money?*, BMJ, Aug. 2012, at 22 (arguing the cost is closer to \$60 million, and explaining why the industry supported figure is an overestimation).

⁵² GUIDANCE FOR INDUSTRY, *supra* note 39, at 13.

study for treating depression may exclude patients who have a history of bipolar disorder, psychosis, or an eating disorder.⁵³ Patients with complex health problems are usually not RCT subjects even though these patients are the ones who may be the most prone to adverse effects.⁵⁴ Indeed, a number of medicines are beneficial for certain conditions and harmful for others.⁵⁵ Patients already taking non-investigational medications may be disqualified from participation because drugs may interact with each other, which presents researchers who seek to test the drug in ideal conditions with an undesirable confounder. These selection practices all implicate concerns about “external validity”—the ability to generalize results to the overall population—and these shortcomings have led a number of researchers to question whether the scientific community over relies on RCTs in drug approval and evidence-based medicine.⁵⁶

Beyond the study design’s intrinsic problems, a growing body of literature indicates that RCTs sponsored by pharmaceutical manufacturers may be biased. Evidence suggests that industry-financed trials, which make up around 80% of all clinical trials,⁵⁷ are more likely to

⁵³ This was the case in a study of citalopram for the treatment of major depressive disorder. This sample would not have been directly relevant for 78% of people suffering from major depressive disorder. Stephen R. Wisniewski et al., *Can Phase III Trial Results of Antidepressant Medications be Generalized to Clinical Practice? A STAR*D Report*, 166 AM. J. PSYCHIATRY 599 (2009).

⁵⁴ Kaplan et al., *supra* note 44.

⁵⁵ As an illustration, diuretics can help with heart failure and pulmonary edema, but may negatively impact kidney function. See Fernando L. Martin et al., *Targeting the Kidney in Acute Decompensated Heart Failure: Conventional Diuretics and Renal-Acting Vasodilators*, 9 REVS. CARDIOVASCULAR MED. 39 (2008).

⁵⁶ See Williams, *supra* note 45, at 109 (noting that RCTs require large numbers of patients to achieve statistically significant results, and that the means of these large samples have weak predictive validity for individual patients); see also Kaplan et al., *supra* note 44 (noting that excessive reliance on RCTs tends to stifle funding of other types of research, and that RCTs have major limitations).

⁵⁷ Lynn M. Etheredge, *A Rapid-Learning Health System*, 26 HEALTH AFF. w107, w109 (2007), available at <http://content.healthaffairs.org/content/26/2/w107.full.pdf+html?sid=eecfaf53-644a-49da-ac27-04a3f1190e7b>.

have results that favor sponsors.⁵⁸ For instance, one meta-analysis (a statistical technique that aggregates research data from multiple studies) found that trials sponsored by a drug manufacturer are 3.6 times more likely to find an investigated drug effective than studies without such ties.⁵⁹ There is “an association, typically a strong one, between industry support and published pro-industry results.”⁶⁰ Trial results are selectively reported in various ways, which can include adding favorable outcomes, deleting unfavorable outcomes, and changing reported outcomes’ statistical significance.⁶¹ Of course, there are a number of innocuous reasons why there may be an association between industry support and favorable results. For example, industry may be more prone to fund studies that seem likely to produce favorable results, or investigators partnered with for-profit companies may have already conducted research suggesting that a drug is efficacious.⁶² However, the powerful financial incentives pharmaceutical manufacturers have to produce positive results creates cause for bias in these studies. In an attempt to compensate for this influence, the FDA requires that all investigators conducting clinical studies disclose their financial incentives.⁶³ Consequently, all major medical journals that publish clinical trial results now require investigators to disclose conflicts of

⁵⁸ INST. OF MED. OF THE NAT’L ACADS., CONFLICT OF INTEREST IN MEDICAL RESEARCH, EDUCATION, AND PRACTICE 23–27 (Bernard Lo & Marilyn J. Field eds., 2009), *available at* <http://www.ncbi.nlm.nih.gov/books/NBK22942/pdf/TOC.pdf>.

⁵⁹ Justin E. Bekelman et al., *Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systematic Review*, 289 JAMA 454 (2003).

⁶⁰ Sergio Sismondo, *Pharmaceutical Company Funding and Its Consequences: A Qualitative Systematic Review*, 29 CONTEMP. CLINICAL TRIALS 109, 112 (2008).

⁶¹ Erick H. Turner et al. *Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy*, 358 NEW ENG. J. MED. 252 (2008).

⁶² INST. OF MED. OF THE NAT’L ACADS., *supra* note 58, at 97–121.

⁶³ *Financial Disclosures by Clinical Investigators*, FDA (Feb. 2, 1998), <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm119145.htm>.

interest, but in practice this does not always occur.⁶⁴

So, while RCTs are the gold standard for evaluating risk–benefit profiles in preapproval testing, they have limits, which is why observational research is also critical.⁶⁵ In fact, the two approaches are complementary; each has its own advantages. For instance, observational studies permit far larger sample sizes than RCTs. Accordingly, observational studies may more accurately reflect clinical practice conditions because they include a broader population.⁶⁶ In other words, observational studies can have greater external validity because they include a more diverse population.⁶⁷ Most of the data used to evaluate risk–benefit profiles in the post-market period are from observational research.⁶⁸ Of course, like RCTs, observational studies have deficiencies; namely, they lack the RCTs’ strength in ensuring internal validity.⁶⁹

1. *EXISTING RESOURCES IN PHARMACOVIGILANCE*

The FDA already uses observational data to internally conduct post-market risk assessment.⁷⁰ The FDA Adverse Event Reporting System (“FAERS”) is a database that contains

⁶⁴ See, e.g., Michelle Roseman et al., *Reporting of Conflicts of Interest from Drug Trials in Cochrane Reviews: Cross Sectional Study*, BMJ, Sept. 2012, at 18 (noting that most Cochrane reviews of drug trials in 2010 failed to disclose trial funding sources and trial author-industry financial ties or employment); see also Joanna K. Sax, *Financial Conflicts of Interest in Science*, 21 ANNALS OF HEALTH L. 291, 300 (2012).

⁶⁵ In fact, some research has found no significant differences in treatment effects between clinical outcome ranges obtained from RCTs and observational data. John Concato et al., *Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs*, 342 NEW ENG. J. MED. 1887 (2000).

⁶⁶ Kaplan et al., *supra* note 44.

⁶⁷ *Id.*

⁶⁸ INST. OF MED. OF THE NAT’L ACADS., *supra* note 37, at 75–76.

⁶⁹ See generally *FDA Adverse Event Reporting System (FAERS) (Formerly AERS)*, FDA, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm> (last updated Sept. 10, 2012) (discussing problems with data in the FAERS system).

⁷⁰ GUIDANCE FOR INDUSTRY, *supra* note 39, at 12–17. The FDA has access to resources including medical literature, clinical trials, and commercial databases with information on the use of

information on adverse event and medication error reports submitted to the FDA.⁷¹ A broad range of stakeholders, including consumers and health care providers, submit reports to the FDA under this largely voluntary system.⁷² However, when manufacturers become aware of adverse events, the FDA mandates that they must submit reports through FAERS.⁷³ The FDA uses FAERS to reveal new safety concerns and to evaluate manufacturers' compliance with reporting regulations.⁷⁴

Case reports obtained through FAERS may prompt further evaluation with larger databases, such as those in the Sentinel System.⁷⁵ The Sentinel System is a national electronic

prescription drugs. CTR. FOR DRUG EVALUATION & RESEARCH, FDA, U.S. DEP'T OF HEALTH & HUMAN SERVS., 2005 REPORT TO THE NATION: IMPROVING PUBLIC HEALTH THROUGH HUMAN DRUGS 37 (2005), *available at* <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/WhatWeDo/ucm078935.pdf>. The FDA also makes use of clinical data submitted post-approval by product sponsors, and may even approve a drug contingently and require the drug sponsor to undertake additional clinical research after market approval. These are referred to as "phase 4 confirmatory trials." *Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review*, FDA, <http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm> (last updated June 26, 2013).

⁷¹ See *FDA Adverse Event Reporting System (FAERS) (Formerly AERS)*, *supra* note 69.

⁷² Reporting certain adverse events is mandatory. See *Drug/Biologic/Human Cell, Tissues and Cellular and Tissue-Based Product Manufacturers, Distributors, and Packers*, FDA, <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm085692.htm> (last updated July 1, 2009).

⁷³ See *FDA Adverse Event Reporting System (FAERS) (Formerly AERS)*, *supra* note 69. The FDA does perform oversight over pharmaceutical manufacturer adverse event reporting. FDA field inspectors visit firms to assess reporting regulation compliance, and the FDA works with firms to correct deficiencies. CTR. FOR DRUG EVALUATION & RESEARCH, *supra* note 70, at 37–38.

⁷⁴ See *FDA Adverse Event Reporting System (FAERS) (Formerly AERS)*, *supra* note 69. FAERS reports are evaluated by clinical researchers in the Center for Drug Evaluation and Research ("CDER") and the Center for Biologics Evaluation and Research ("CBER"). CDER and CBER are FDA Centers that regulate over-the-counter and prescription drugs, including biological therapeutics and generic drugs. *About the Center for Drug Evaluation and Research*, FDA, <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm> (last updated May 9, 2013).

⁷⁵ Likewise, in January 2007, CDER launched the Document Archiving, Reporting, and

system that the FDA launched in May 2008 to track the safety of products in the market.⁷⁶ It allows the FDA to actively query diverse automated health care data holders—including EMR systems, insurance claim databases, and registries—to evaluate product safety issues. In 2012, it achieved the capacity to monitor adverse events in over 100 million U.S. residents.⁷⁷ However, in the years since its initial launch it has yet to generate a significant number of appropriated adjusted analyses of drug risks.⁷⁸ “[F]ull activation by regulatory authorities has lagged,”⁷⁹ and a lack of funding threatens its effectiveness.⁸⁰

Although the FDA evaluates adverse events on a case-by-case basis, it can also

Regulatory Tracking System (“DARRTS”), which centralizes tracking of post-market safety issues. CTR. FOR DRUG EVALUATION & RESEARCH, FDA, U.S. DEP’T OF HEALTH & HUMAN SERVS., GUIDANCE: CLASSIFYING SIGNIFICANT POSTMARKETING DRUG SAFETY ISSUES 2 (2012), *available at*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM295211.pdf>. The system enables information sharing across multiple FDA offices. Since its inception, almost 1000 tracked safety issues have been entered. *Id.* at 3.

⁷⁶ For an overview of the Sentinel pilot system, the Mini-Sentinel, see Richard Platt et al., *The U.S. Food and Drug Administration’s Mini-Sentinel Program: Status and Direction*, 21 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 1 (2012); Barbara J. Evans, *The Ethics of Postmarketing Observational Studies of Drug Safety Under Section 505(o)(3) of the Food, Drug, and Cosmetic Act*, 38 AM. J.L. & MED. 577, 583, 599, 604–05 (2012).

⁷⁷ Aaron S. Kesselheim et al., *Who Is Now Responsible for Discovering and Warning About Adverse Effects of Generic Drugs?*, JAMA, at E2 (Aug. 5, 2013), <http://jama.jamanetwork.com.proxy.lib.uiowa.edu/article.aspx?articleid=1724479>.

⁷⁸ *Id.*

⁷⁹ Jerry Avorn, *The Promise of Pharmacoepidemiology in Helping Clinicians Assess Drug Risk*, 128 CIRCULATION 745, 747 (2013).

⁸⁰ See Kesselheim, *supra* note 77, at E2. The system is still under development and the FDA is implementing it in stages. On January 31, 2013, Janet Woodcock, director of the FDA’s Center for Drug Evaluation and Research, stated “that once the [Sentinel System] reaches its full potential, it could ‘revolutionize’ product safety.” Bronwyn Mixter, *Safety: FDA’s Sentinel Initiative Could Revolutionize Product Safety; Funding Needed, Official Says*, MED. DEVICES L. & INDUSTRY REP., Feb. 6, 2013, *available at* Bloomberg BNA: Health Law Res. Ctr., 7 MELR 81. The Sentinel System is another potential resource for the administrative bounty proceeding proposed in this Article.

systematically examine databases using statistical analyses—this is called “data mining.”⁸¹ Data mining may allow the FDA to identify unusual or unexpected product-event combinations warranting further investigation.⁸² For example, the Multi-Item Gamma Poisson Shrinker (“MGPS”) is the data-mining algorithm that the FDA uses to analyze FAERS and to look at drug-drug interactions.⁸³ To detect a signal,⁸⁴ MGPS examines the ratio of an observed adverse effect to the total number of adverse events. The MGPS algorithm has been shown to identify most adverse events one to five years prior to detection by standard methods.⁸⁵

These resources have limits, however, because voluntary adverse event reporting systems are susceptible to biases. First, in addition to problems related to internal validity, these reports do not always contain enough detail to properly evaluate the adverse event. Second, not all adverse events are reported because patients and providers may not recognize that an adverse event is the result of a drug, and adverse events that occur rarely or over relatively long time periods may be particularly challenging to recognize. Third, there is no guarantee that reported

⁸¹ GUIDANCE FOR INDUSTRY, *supra* note 39, at 8–10; *see* Ismaïl Ahmed et al., *Early Detection of Pharmacovigilance Signals with Automated Methods Based on False Discovery Rates: A Comparative Study*, 35 DRUG SAFETY 495, 496 (2012) (“Our results show that as soon as there is reasonable support for the data, automated signal detection tools are powerful tools to explore large spontaneous reporting system databases and detect relevant signals quickly compared with traditional pharmacovigilance methods.”).

⁸² Statistical techniques used for data mining include cluster analysis, link analysis, deviation detection, and disproportionality assessment, which can be used to detect the presence and strength of adverse drug event signals. For a discussion of these techniques and their applicability to data mining, *see* Andrew M. Wilson et al., *Application of Data Mining Techniques in Pharmacovigilance*, 57 BRIT. J. CLINICAL PHARMACOLOGY 127 (2004).

⁸³ Robert D. Gibbons et al., *Post-Approval Drug Safety Surveillance*, 31 ANN. REV. PUB. HEALTH 419 (2010).

⁸⁴ According to the FDA, a “safety signal refers to a concern about an excess of adverse events compared to what would be expected to be associated with a product’s use.” GUIDANCE FOR INDUSTRY, *supra* note 39, at 4.

⁸⁵ Ana Szarfman et al., *Use of Screening Algorithms and Computer Systems to Efficiently Signal Higher-Than-Expected Combinations of Drugs and Events in the US FDA’s Spontaneous Reports Database*, 25 DRUG SAFETY 381, 390 (2002).

events are the result of product use, since the FDA's reporting system does not require a proven relationship between a product and an event. Indeed, that would defeat much of the reporting system's purpose. The drawback is that adverse events may be incidental to the product's use. Fourth, reports may be suspect when submitted due to improper motives, such as to support litigation.⁸⁶ Clinical trials, which likely involve a relatively high degree of oversight and high-quality reporting, avoid many of these shortcomings of observational studies. Taking these caveats into account, when the FDA determines that the available data justifies regulatory action, it may require manufacturers to amend labeling information, restrict use of the drug, communicate new safety information to the public, or remove a product from the market.⁸⁷

The public does not have unrestricted access to the FDA's data, but the FDA does provide the number of reports it has received for products over the past decade, and persons familiar with relational database creation can extract raw data from individual case safety reports.⁸⁸ Also, the public can obtain individual case safety reports from FAERS through a Freedom of Information ("FOI") request to the FDA.⁸⁹ Finally, the FDA publishes quarterly reports on potential serious side effects identified by FAERS and summarizes information about

⁸⁶ GUIDANCE FOR INDUSTRY, *supra* note 39, at 9.

⁸⁷ SUSAN THAUL, CONG. RESEARCH SERV., R41983, HOW FDA APPROVES DRUGS AND REGULATES THEIR SAFETY AND EFFECTIVENESS 8–19 (2012), *available at* <http://www.fas.org/sgp/crs/misc/R41983.pdf>.

⁸⁸ *See FDA Adverse Reporting System (FAERS) (Formerly AERS)*, *supra* note 69 ("FAERS Data Files: provides raw data consisting of individual case safety reports extracted from the FAERS database. A simple search of FAERS data cannot be performed with these files by persons who are not familiar with creation of relational databases."). Ted Codd at IBM created the relational model of data in the 1960s and 1970s as a solution to the problem of managing large commercial databases. S. SUMATHI & S. ESAKKIRAJAN, FUNDAMENTALS OF RELATIONAL DATABASE MANAGEMENT SYSTEMS 728 (2007). Relational databases associate information by means of a common field. Relational databases now form the majority of large databases. *See generally id.*

⁸⁹ *FDA Adverse Event Reporting System (FAERS) (Formerly AERS)*, *supra* note 69.

ongoing and completed post-market safety evaluations of adverse experience reports.⁹⁰

1. *REGULATORY SHORTCOMINGS*

The FDA has a difficult job. It is no easy matter to evaluate a drug's safety and efficacy. Its task is all the more complex given the unknowns about disease and pharmacology, the American population's vast diversity, and the range of products submitted for evaluation. Even so, some argue the FDA is overburdened.⁹¹ Agency criticism was particularly acute in the first years of the twenty-first century, after a series of drug withdrawals, delays in warning the public about drug risks, and well-publicized disputes within the agency created a public perception that the FDA was rushing to approve drugs without sufficient attention.⁹² At the same time, industry and patient advocate groups complained about slow processing times and the agency's "risk-adverse" nature.⁹³

Although manufacturers have withdrawn a number of drugs from the market in recent years, typically in close consultation with the FDA, no withdrawal attracted more negative attention to the FDA than withdrawal of Vioxx (rofecoxib), which was not only the largest drug withdrawal in history, but also prompted thousands of lawsuits against its manufacturer, Merck & Co., Inc. ("Merck"), and a series of congressional hearings on the safety of FDA-approved drugs.⁹⁴

⁹⁰ *Id.*

⁹¹ See John T. Aquino, *Drug Development: Panel's Focus on Challenges Puts Damper on Session on Life Sciences' 'Bright Future,'* LIFE SCI. L. & INDUSTRY REP., Oct. 5, 2012, available at Bloomberg BNA: Health Law Res. Ctr., 6 LSLR 1023.

⁹² INST. OF MED. OF THE NAT'L ACADS., *supra* note 37, at 1–2.

⁹³ Aquino, *supra* note 91.

⁹⁴ For example, drugs withdrawn from the market after receiving FDA approval since 2000 include Xigris, Meridia, Darvon/Darvocet, Mylotarg, Trasylol, Raptiva, Permax, Zelnorm, NeutroSpec, Palladone, Bextra, Orlaam, Baycol, and Raplon. MARJORIE POWELL, PHRMA, DRUG PRODUCTS THAT HAVE BEEN WITHDRAWN FROM THE U.S. MARKET (2012), available at

The FDA approved Vioxx in May 1999 as a treatment for osteoarthritis and menstrual pain.⁹⁵ The drug received expedited approval through the priority review system because it potentially provided a significant benefit over existing therapies, which primarily consisted of non-steroidal anti-inflammatory drugs (“NSAID”s).⁹⁶ Unfortunately, all drugs have side-effects, and NSAIDs are no exception. Long-term use of NSAIDs, such as ibuprofen and naproxen, can cause serious gastrointestinal side effects, including life-threatening bleeding.⁹⁷ Vioxx, on the other hand, was part of a newer class of medicines (COX-2 selective) that potentially had a lower risk of causing bleeding events.⁹⁸ The safety database the FDA used to evaluate the drug included approximately 5000 patients, and according to the FDA it “did not show an increased risk of heart attack or stroke.”⁹⁹

<http://www.ncleg.net/documentsites/committees/senatejudiciaryi2011/Subcommittee%20on%20Pharmaceutical%20Liability/March%2029,%202012%20Meeting/Information%20Obtained%20in%20Response%20to%20Questions%20from%20February%2021%20Meeting/Powell%20response%20-%20Withdrawals%202000%20to%202011.pdf>.

⁹⁵ The FDA’s approval letter for Vioxx is available on the FDA’s website. Letter from Robert J. DeLap, Dir. Office of Drug Evaluation, to Robert E. Silverman, Senior Dir., Regulatory Affairs, Merck Research Labs. (May 20, 1999), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/021042_52_vioxx_appltr.pdf. The original label is also available. *Vioxx® (Rofecoxib Tablets and Oral Suspension)*, FDA, http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/021042_52_vioxx_prntlbl.pdf (last visited Aug. 23, 2013).

⁹⁶ *Vioxx: Hearing Before the S. Comm. on Finance*, 108th Cong. (2004) (statement of Sandra Kweder, Deputy Dir., Office of New Drugs, Ctr. for Drug Evaluation and Research, FDA, Dep’t of Health & Human Servs.), *available at* <http://www.hhs.gov/asl/testify/t041118d.html>. Under the Prescription Drug User Fee Act (“PDUFA”), a two-tiered review system was established within the FDA. Standard review is applied to drugs that offer minor improvements over products already on the market (“me-too” drugs), while priority review is applied to drugs that offer major advances in treatment or treat an orphan condition (a condition which affects fewer than 200,000 individuals in the U.S.). *Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review*, *supra* note 70.

⁹⁷ David Y. Graham et al., *Visible Small-Intestinal Mucosal Injury in Chronic NSAID Users*, 3 CLINICAL GASTROENTEROLOGY & HEPATOLOGY 55 (2005).

⁹⁸ *Vioxx: Hearing Before the S. Comm. on Finance*, *supra* note 96.

⁹⁹ *Id.*

After the FDA approved Vioxx, Merck engaged in an aggressive, and very successful, direct-to-consumer advertising and physician detailing campaign.¹⁰⁰ The drug soon became a “blockbuster,” which is a drug that earns more than \$1 billion a year in the United States.¹⁰¹ While it marketed Vioxx, Merck continued to perform clinical trials to evaluate Vioxx’s gastrointestinal toxicity and long-term clinical outcomes. The largest of these studies was the Vioxx Gastrointestinal Outcomes Research, or VIGOR study, which evaluated approximately 8000 patients in an arthritic population who were using either Vioxx or naproxen.¹⁰² The results of the VIGOR study showed that patients in the Vioxx group had a five-fold increase in the rate of heart attacks compared to patients in the naproxen group.¹⁰³ However, Merck argued to the FDA that the differences between the groups were due to a protective effect of naproxen, rather than to a risk inherent in Vioxx.¹⁰⁴ As a result, the FDA approved labeling changes based on the

¹⁰⁰ Physician detailing refers to pharmaceutical sales representatives visiting physicians to promote their firm’s drugs. Brand-name manufacturers commit significant resources to detailing efforts. “[T]he average primary care physician interacts with no fewer than twenty-eight detailers each week and the average specialist interacts with fourteen.” *IMS Health Inc. v. Ayotte*, 550 F.3d 42, 47 (1st Cir. 2008), *abrogated by Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011). Pharmaceutical companies spend \$25,000 per physician annually on detailing. Amanda L. Connors, Comment, *Big Bad Pharma: An Ethical Analysis of Physician-Directed and Consumer-Directed Marketing Tactics*, 73 ALB. L. REV. 243, 255 (2009). The Congressional Budget Office has noted that brand-name pharmaceutical manufacturers spent \$12 billion in 2008 on detailing. SHEILA CAMPBELL, MICROECONOMICS STUDIES DIV., CONG. BUDGET OFFICE, PROMOTIONAL SPENDING FOR PRESCRIPTION DRUGS 2 (2009), *available at* http://www.cbo.gov/sites/default/files/cbofiles/ftpdocs/105xx/doc10522/12-02-drugpromo_brief.pdf. This is more than they spend on direct-to-consumer advertising. *See* Connors, *supra*, at 271.

¹⁰¹ Bruce Patsner, *The Vioxx Settlement: Salvation or Sell-Out?*, HEALTH L. PERSP., Feb. 26, 2008, at 1–2 & n.10, *available at* [http://www.law.uh.edu/healthlaw/perspectives/2008/\(BP\)%20vioxx.pdf](http://www.law.uh.edu/healthlaw/perspectives/2008/(BP)%20vioxx.pdf).

¹⁰² The participation criteria excluded patients taking aspirin for cardiovascular protection, because aspirin can also cause intestinal bleeding and might have confounded the results.

¹⁰³ Henry A. Waxman, *The Lessons of Vioxx—Drug Safety and Sales*, 352 NEW ENG. J. MED. 2576, 2577 (2005).

¹⁰⁴ *Id.*

VIGOR study's findings, but there has been controversy surrounding the negotiation process and the adequacy of the warning.¹⁰⁵

Eventually, largely independent retrospective observational studies found that Vioxx caused an increased risk for cardiovascular events.¹⁰⁶ In response, Merck elected to voluntarily remove Vioxx from the market on September 30, 2004.¹⁰⁷ By that time, the drug was earning more than "\$2.5 billion a year, of which \$2 billion were profits (the gross margin was 80% in 2013)."¹⁰⁸ When Merck withdrew the drug from market, its CEO Raymond Gilmartin stated that Merck was "really putting patient safety first,"¹⁰⁹ after unexpectedly finding an increase in heart attack and stroke risk in recent study findings.¹¹⁰ By then, more than 100 million prescriptions for Vioxx had been filled,¹¹¹ and it was estimated that Vioxx had caused between 88,000 and 140,000 excess cases of serious coronary heart disease during its market life.¹¹²

Later, an onslaught of litigation brought to light Merck's concern about the risk of cardiovascular effects long before the drug was approved. One internal Merck memo warned that

¹⁰⁵ Margaret Gilhooley, *Vioxx's History and the Need for Better Procedures and Better Testing*, 37 SETON HALL L. REV. 941, 948–49 (2007).

¹⁰⁶ Memorandum from David J. Graham, Assoc. Dir. for Sci., Office of Drug Safety, to Paul Seligman, Acting Dir., Office of Drug Safety 13 (Sept. 30, 2004), *available at* http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1_30_EE-FDA-Tab-S.pdf.

¹⁰⁷ *Vioxx (Rofecoxib) Questions and Answers*, FDA (Sept. 30, 2004), <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106290.htm>.

¹⁰⁸ Kurt W. Rotthoff, *Product Liability Litigation: An Issue of Merck and Lawsuits over Vioxx*, 20 APPLIED FIN. ECON. 1867, 1874 (2010).

¹⁰⁹ Anna Wilde Mathews & Barbara Martinez, *E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage*, WALL ST. J. (Nov. 1, 2004), <http://online.wsj.com/article/0,,SB109926864290160719,00.html> (internal quotation marks omitted).

¹¹⁰ *Id.*

¹¹¹ Waxman, *supra* note 103, at 2576.

¹¹² David J. Graham et al., *Risk of Acute Myocardial Infarction and Sudden Cardiac Death in Patients Treated with Cyclo-Oxygenase 2 Selective and Non-selective Non-steroidal Anti-inflammatory Drugs: Nested Case-Control Study*, 365 LANCET 475, 480 (2005).

Vioxx studies should only include patients taking aspirin, otherwise there would be a “substantial chance that significantly higher rates’ of cardiovascular disease would show up in the Vioxx® group.”¹¹³ Also, Merck’s research chief had e-mailed colleagues that the cardiovascular events “are clearly there” and called it a “shame.”¹¹⁴ Evidence that Merck had clinical evidence demonstrating an increased risk of adverse cardiovascular effects for Vioxx prior to its marketing that it did not share with the FDA was particularly damaging in litigation. In 2007, Merck agreed to pay \$4.85 billion to settle approximately 26,000 cases brought by patients who had suffered severe adverse effects after taking Vioxx.¹¹⁵ While this may seem like a large sum, it is substantially less than many commentators had predicted.¹¹⁶ This settlement was widely regarded as a significant victory for Merck.¹¹⁷ In November 2011, Merck additionally entered into a civil settlement agreement with the government in which it was

¹¹³ FREDERICK M. ABBOTT & GRAHAM DUKES, *GLOBAL PHARMACEUTICAL POLICY: ENSURING MEDICINES FOR TOMORROW’S WORLD* 207 (2009).

¹¹⁴ Mathews & Martinez, *supra* note 109 (internal quotation marks omitted for both quotations).

¹¹⁵ Settlement Agreement Between Merck & Co., Inc. and the Counsel Listed on the Signature Pages Hereto 1–2 (Nov. 9, 2007), *available at* http://hosted.ap.org/specials/interactives/_documents/vioxx_settlement_agreement.pdf; *see also* Linda A. Johnson, *Merck to Start Vioxx Settlement Payouts in August*, BEASLEY ALLEN (July 17, 2008), <http://www.beasleyallen.com/news/merck-to-start-vioxx-settlement-payouts-in-august/>. Merck also spent \$1.53 billion on legal costs and individual trials, most of which it won. Johnson, *supra*. Merck may still face additional liability from claimants who did not opt into the settlement program, although more than 99.9% of eligible patients have opted in. *In re Vioxx Prods. Liab. Litig.*, 760 F. Supp. 2d 640, 646 (E.D. La. 2010).

¹¹⁶ A potential liability of \$30 billion was widely touted. *See, e.g.*, BRYAN HELLER & PETER LAVALLEE, YALE SCH. OF MGMT., *MERCK & CO., INC.* (2005), *available at* <http://analystreports.som.yale.edu/reports/merck.pdf>; CATHERINE PICHEREAU, *VIOXX: LIFTING THE VEIL ON THE DARK SIDE OF THE PHARMACEUTICAL INDUSTRY* (2005), *available at* <http://www.bionest.com/publications/Vioxx.pdf>.

¹¹⁷ In the final analysis, the decision to keep Vioxx on the market until 2004 may have resulted in net profit for the company. Rothoff, *supra* note 108, at 1868–69. Despite all of Merck’s troubles with Vioxx, the company made more than \$4.6 billion in profits in 2005. *Message to Shareholders*, MERCK SHARP & DOHME CORP. (Feb. 22, 2006), http://www.merck.com/finance/annualreport/ar2005/message_to_shareholders.html#financial_highlights.

required to pay more than \$628 million to resolve allegations regarding off-label marketing of Vioxx and false statements about the drug's cardiovascular safety.¹¹⁸ A month later, Merck was sentenced to pay a criminal fine of more than \$321 million in connection with a guilty plea related to its marketing of Vioxx.¹¹⁹

In the end, Vioxx had an unfavorable risk–benefit profile and was withdrawn from the market. The data that Merck had worked diligently to suppress was made public, and many injured patients received substantial settlements.¹²⁰ Yet these outcomes were not optimal; the system should have intervened sooner to protect public health.¹²¹ The potential for tort liability was apparently not enough to incentivize Merck to act in the public's best interest.¹²²

¹¹⁸ *U.S. Pharmaceutical Company Merck Sharp & Dohme Sentenced in Connection with Unlawful Promotion of Vioxx*, U.S. DEP'T OF JUSTICE (Apr. 19, 2012), <http://www.justice.gov/opa/pr/2012/April/12-civ-497.html>. Of this amount, the federal government will recover approximately \$426 million, and \$202 million will be distributed to participating Medicaid States. *Id.* The settlement resolved allegations that Merck made misleading statements about Vioxx's cardiovascular safety to increase drug sales, resulting in payments by the federal government and state Medicaid agencies. *Id.*

¹¹⁹ *Id.* The criminal plea was related to Merck's misbranding of Vioxx and promotion of the drug for treating rheumatoid arthritis before the FDA approved that indication in 2002. *Id.*

¹²⁰ Snigdha Prakash, *Part 1: Documents Suggest Merck Tried to Censor Vioxx Critics*, NPR (June 9, 2005, 12:00 AM), <http://www.npr.org/templates/story/story.php?storyId=4696609>.

¹²¹ Peter Jüni et al., *Risk of Cardiovascular Events and Rofecoxib: Cumulative Meta-Analysis*, 364 LANCET 2021, 2021 (2004) ("Our findings indicate that rofecoxib should have been withdrawn several years earlier."); see also Rhema Vaithianathan et al., *Iatrogenic Effects of COX-2 Inhibitors in the US Population: Findings from the Medical Expenditure Panel Survey*, 32 DRUG SAFETY 335, 336 (2009) ("Drugs that were rapidly accepted for assumed safety advantages proved instead to have caused substantial injury and death.").

¹²² Among the many ways in which Merck behaved badly in this debacle, once evidence of the negative cardiovascular effects of Vioxx became more apparent, the company engaged in a campaign of threats and intimidation to attempt to silence its critics. Several top medical schools reported "a consistent pattern of intimidation of investigators by Merck." JUSTIN BIDDLE, *ADVERSARIAL SYSTEMS AND THE PRIVATIZATION OF BIOMEDICAL RESEARCH: AN EPISTEMIC EVALUATION* 11 (2008) (internal quotation marks omitted), available at <http://www2.lse.ac.uk/CPNSS/projects/CoreResearchProjects/ContingencyDissentInScience/DP/BiddleOnlineDP0209.pdf>. As one specific example, Merck sued a medical researcher in Spain, Dr. Joan-Ramon Laporte, to demand he retract an article he had published that was critical of

Merck is not alone in this; a rational actor may have the incentive to risk tort liability if a product stands to deliver profits relative to the litigation costs and damages. Long before Vioxx, the FDA approved the drug MER-29, which was advertised by the Richardson-Merrell group “as the ‘first safe’ drug to lower cholesterol.”¹²³ After the medical community widely accepted MER-29, evidence began to emerge that the drug caused cataracts, baldness, severe dermatitis, and other side effects.¹²⁴ These revelations resulted in the company voluntarily withdrawing the drug from the market.¹²⁵ A week before the drug was withdrawn, the FDA inspected Merrell’s records and found that the company had misrepresented its pre-market data.¹²⁶ Even though the company was fined \$80,000, and later paid out an estimated \$200 million in civil damages, these costs amounted to just a fraction of the drug’s \$4.25 billion in annual sales.¹²⁷ Today, an absence of strong deterrents may continue to incentivize commercial malfeasance.

The Vioxx saga may be a case study of bad corporate behavior, but the FDA bears responsibility for failure to intervene sooner. In part, this was due to the fact that the FDA lacks private industry’s resources.¹²⁸ The agency’s tools for gathering post-approval information have been characterized as “relatively crude and ineffective . . . they amount only to a tiny fraction of

Vioxx. *Id.* The court eventually ruled in Dr. Laporte’s favor. *Id.* A few months later, it was announced he was scheduled to be the featured speaker at an annual conference for family doctors that Merck had sponsored for eight years. *Id.* After the announcement, Merck contacted the conference organizer and requested that Dr. Laporte be excluded from the program. *Id.* After the organizer refused, “Merck withdrew its financing—about \$140,000.” *Id.*

¹²³ Paul D. Rheingold, *The MER/29 Story—An Instance of Successful Mass Disaster Litigation*, 56 CALIF. L. REV. 116, 120 (1968).

¹²⁴ *Id.*

¹²⁵ *Id.*

¹²⁶ *Id.* The FDA was also criticized for lax oversight in the MER-29 debacle. *Id.* at 118–19.

¹²⁷ PHILLIP KNIGHTLEY ET AL., *SUFFER THE CHILDREN: THE STORY OF THALIDOMIDE* 65 (1979).

¹²⁸ ABBOTT & DUKES, *supra* note 113, at 203.

those available to industry.”¹²⁹ The Institute of Medicine (“IOM”) conducted a major independent assessment in the wake of the Vioxx scandal’s congressional hearings, which found that the FDA is “severely underfunded,” and its shortcomings hinder its ability to evaluate the safety of drugs.¹³⁰

Criticisms of the FDA have not been limited to its actions regarding Vioxx. For example, in 2007, the FDA Science Board found that escalating demands combined with inadequate funding impaired the FDA’s ability to keep pace with scientific advances, product complexity, and industry globalization.¹³¹ In 2011, a major report by the Government Accountability Office (“GAO”) on the FDA’s pre-market review and post-market safety efforts for medical devices identified several gaps in the FDA’s ability to “proactively identify and address the risks presented by unsafe devices . . . [and] ensure that the highest-risk recalls were implemented in an effective and timely manner.”¹³² The report concluded that the “GAO’s preliminary work suggests that the combined effect of these gaps may increase the risk that unsafe medical devices could remain on the market.”¹³³ Following up on the FDA Science Board report, on November 19, 2012, the Partnership for Public Service published a finding that the FDA had systemic workforce failures and noted that “the hiring process [took] far too long to bring new talent

¹²⁹ *Id.*

¹³⁰ See INST. OF MED. OF THE NAT’L ACADS., *supra* note 37, at 193.

¹³¹ FDA SCI. BD., SUBCOMM. ON SCI. & TECH., FDA SCIENCE AND MISSION AT RISK 1–5 (2007), *available at* http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf.

¹³² U.S. GOV’T ACCOUNTABILITY OFFICE, GAO-11-468, MEDICAL DEVICES: FDA SHOULD ENHANCE ITS OVERSIGHT OF RECALLS (2011), *available at* <http://www.gao.gov/assets/320/319565.pdf>.

¹³³ U.S. GOV’T ACCOUNTABILITY OFFICE, GAO-11-556T, FDA’S PREMARKET REVIEW AND POSTMARKET SAFETY EFFORTS (2011), *available at* <http://www.gao.gov/assets/130/126013.pdf>.

onboard and too often [did] not deliver quality candidates.”¹³⁴ On the same day, the Office of Inspector General (“OIG”) released its report, *Top Management and Performance Challenges Facing the Department of Health and Human Services in Fiscal Year 2012*. The OIG’s report identified oversight of the FDA as a top management challenge. It named several vulnerabilities within the FDA, including inadequate monitoring of off-label use, weakness in management of internal scientific disagreements, and a need to improve oversight of drug and device regulatory decisions.¹³⁵ Taken together, these reports expose fundamental concerns about the FDA’s ability to regulate drug safety effectively without external assistance.

Because of its limited capacity, the FDA relies on pharmaceutical manufacturers to play a central role in pharmacovigilance. That, however, leads to a deeply unbalanced regulatory model since product sponsors have an incentive to selectively report favorable findings. Furthermore, the FDA lacks the ability to adequately compel sponsors to complete appropriate post-market studies.¹³⁶ During congressional hearings, it was noted that out of 1231 agreed-on (by the sponsor) open post-market commitment studies of drugs and biologics, 797 (65%) had yet to be

¹³⁴ P’SHIP FOR PUB. SERV., THE STATE OF THE FDA WORKFORCE 3 (2012), *available at* <http://ourpublicservice.org/OPS/publications/viewcontentdetails.php?id=215>.

¹³⁵ 2012 *Top Management & Performance Challenges*, OFF. INSPECTOR GEN., <https://oig.hhs.gov/reports-and-publications/top-challenges/2012/> (last visited Aug. 23, 2013).

¹³⁶ The Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823, granted the FDA authority to require additional post-market studies, and to impose fines if a sponsor fails to comply with the FDA’s post-market study requirements. However, the FDA can only require studies if information reveals an “unexpected serious risk” that cannot be addressed through other controls. *Id.* § 901(a). This leaves “substantial” surveillance gaps. David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA’s Efforts to Preempt Failure-to-Warn Claims*, 96 GEO. L.J. 461, 495 (2008). Post-market clinical trials can only be required if post-market observational trials are insufficient. Food and Drug Administration Amendments Act of 2007 § 901(a). The FDA may also compel label changes, but only after first negotiating with a drug sponsor. Kessler & Vladeck, *supra*, at 466 n.17.

started.¹³⁷ Additionally, potential conflicts of interest within the FDA are troubling. The IOM report found that the nominally independent scientific expertise relied on by the FDA may have been biased, and the FDA's dependence on user fee funding raises the possibility of undue industry influence.¹³⁸ Nearly half of the FDA's budget to review new drugs comes from user fees.¹³⁹

B. THE STRUGGLE FOR ACCEPTANCE

1. HEALTH INFORMATION TECHNOLOGY AND HEALTH INFORMATION EXCHANGE

There is a longstanding and widely held belief in the medical community that using health information technology ("HIT"), which involves the exchange of clinical data in an electronic environment, benefits patient care.¹⁴⁰ Evidence suggests that HIT can make health care delivery more efficient, cost-effective, and safe because it makes practice guidelines and evidence databases available to health care providers and improves computerized patient record

¹³⁷ Report on the Performance of Drug and Biologics Firms in Conducting Postmarketing Commitment Studies, 71 Fed. Reg. 10,978, 10,978–79 (Mar. 3, 2006), *available at* <http://www.gpo.gov/fdsys/pkg/FR-2006-03-03/pdf/E6-3019.pdf>.

¹³⁸ INST. OF MED. OF THE NAT'L ACADS., *supra* note 37, at 15–28. Potentially troubling connections to industry are not limited to the FDA; "[t]he integrity of the academic research enterprise has also been questioned, as universities and scientists are increasingly dependent on industry funding." *Id.* at 18.

¹³⁹ The FDA's reliance on user fees paid by industry has also troubled numerous commentators. *See, e.g.*, Amanda Gardner, *FDA Seeks Higher Fees from Drug Industry*, WASH. POST (Jan. 11, 2007, 12:00 AM), <http://www.washingtonpost.com/wp-dyn/content/article/2007/01/11/AR2007011101186.html>. The Prescription Drug User Fee Act ("PDUFA") funds 42% of the budget of Center for Drug Evaluation and Research ("CDER"), the FDA division responsible for analyzing a drug's risks and benefits throughout its lifecycle. Rob Cunningham, *PHARMA: PDUFA Reauthorization: Has Success Spoiled User Fees?*, HEALTH AFF. BLOG (Apr. 18, 2007), <http://healthaffairs.org/blog/2007/04/18/pharma-pdufa-reauthorization-has-success-spoiled-user-fees/>.

¹⁴⁰ HEALTH, BIOMEDICAL SCI. & SOC'Y INITIATIVE, ADOPTERS OF HEALTH INFORMATION TECHNOLOGY START TO SEE ITS BENEFITS 1 (2012), *available at* http://www.aspeninstitute.org/sites/default/files/content/docs/pubs/HIT_Policy_Brief_Final_Aug_2012.pdf.

accessibility.¹⁴¹ It can also help providers communicate with patients, and since HIT improves information access, it encourages patients to participate in their own care.¹⁴² In 2011, the Office of National Coordinator for Health Information Technology (“ONC”) reviewed HIT literature and found that 92% of recent HIT articles reached overall positive conclusions about its use.¹⁴³

Despite extensive research that found that HIT use is beneficial,¹⁴⁴ provider and hospital adoption has been slow.¹⁴⁵ For example, a 2009 study of electronic medical record (“EMR”) use in U.S. hospitals found that only 1.5% of hospitals had a comprehensive EMR system (one that is present in all clinical units), and an additional 7.6% had a basic system (present in at least one clinical unit).¹⁴⁶ At the time, only 17% of hospitals used computerized provider-order entry for medications.¹⁴⁷ Providers’ failure to embrace HIT has led to pervasive criticism; commentators have described the U.S. health care industry as “the world’s largest, most inefficient information enterprise.”¹⁴⁸ Providers generally report they have been slow to adopt HIT for financial reasons, since transitioning to electronic systems often entails high up-front costs for training and new

¹⁴¹ S. CAL. EVIDENCE-BASED PRACTICE CTR., EVIDENCE REPORT/TECHNOLOGY ASSESSMENT NUMBER 132: COSTS AND BENEFITS OF HEALTH INFORMATION TECHNOLOGY 1 (2006), *available at* <http://www.ahrq.gov/downloads/pub/evidence/pdf/hitsyscosts/hitsys.pdf>.

¹⁴² HEALTH, BIOMEDICAL SCI. & SOC’Y INITIATIVE, *supra* note 140, at 1.

¹⁴³ Melinda Beeuwkes Buntin et al., *The Benefits of Health Information Technology: A Review of the Recent Literature Shows Predominantly Positive Results*, 30 HEALTH AFF. 464 (2011).

¹⁴⁴ Ashish K. Jha et al., *Use of Electronic Health Records in U.S. Hospitals*, 360 NEW ENG. J. MED. 1628 (2009).

¹⁴⁵ Catherine M. DesRoches et al., *Electronic Health Records in Ambulatory Care—A National Survey of Physicians*, 359 NEW ENG. J. MED. 50 (2008).

¹⁴⁶ Jha, *supra* note 144, at 1628.

¹⁴⁷ *Id.*

¹⁴⁸ Richard Hillestad et al., *Can Electronic Medical Record Systems Transform Health Care? Potential Health Benefits, Savings, and Costs*, 24 HEALTH AFF. 1103, 1103 (2005) (comparing use of IT in health care to other industries and concluding that the effective implementation of EMR and networking could save more than \$81 billion annually).

infrastructure.¹⁴⁹ Additional barriers to HIT adoption include a lack of interoperability between different HIT systems, the absence of adequate information exchange infrastructure, and the challenges that accompany the use of new technologies.¹⁵⁰

HIT has also faced major challenges in the area of health information exchange (“HIE”)—the ability to exchange real-time health information.¹⁵¹ Most HIT only shares information within a closed network of providers who work together, for instance, in a health maintenance organization (“HMO”) such as Kaiser Permanente. While even this level of data sharing can provide significant benefits, it fails to utilize HIT to its maximum potential. From a clinical perspective, the lack of information sharing between unrelated providers can be a serious problem. As an illustration, a patient might be seen one week at a hospital and receive an extensive (and highly costly) workup, only to present the next week at a different hospital that has to repeat the entire process. Effective HIE promises a solution to this problem because it could allow physicians anywhere to access a patient’s medical records in their entirety through a centralized database.

In addition to the obvious benefits of using HIE to share patient-specific health information with individual providers, so-called “primary uses,” HIE offers benefits outside of direct health care delivery, including quality and safety measurement, pay-for-performance

¹⁴⁹ Jha, *supra* note 144, at 1632.

¹⁵⁰ Julia Adler-Milstein et al., *U.S. Regional Health Information Organizations: Progress and Challenges*, 28 HEALTH AFF. 483 (2009).

¹⁵¹ See SHEERA ROSENFELD ET AL., AVALERE HEALTH LLC, EVOLUTION OF STATE HEALTH INFORMATION EXCHANGE: A STUDY OF VISION, STRATEGY, AND PROGRESS 3 (2006), *available at* http://www.avalerehealth.net/research/docs/State_based_Health_Information_Exchange_Final_Report.pdf. HIE also refers to “[t]he electronic sharing of health information among organizations,” or to “organization[s] that provide services to enable the electronic sharing of health-related information.” *Compatibility & Information Exchange: Health Information Exchange*, HEALTHIT.GOV, <http://www.healthit.gov/providers-professionals/health-information-exchange> (last visited Aug. 23, 2013).

incentive programs, provider certification, clinical research, marketing, and new drug research and development.¹⁵² Of course, even in HIT's absence, health information may be used for secondary purposes. For example, hospitals use paper health care records to perform clinical audits to support quality improvement.¹⁵³ However, certain secondary uses require very large datasets which may be impracticable to acquire without HIE. Secondary HIT use has been particularly critical in the field of epidemiology, in which researchers measure the incidence and prevalence of disease.¹⁵⁴ For instance, large patient databases can help to determine patterns in distribution and determinants of the incidence of cancer.¹⁵⁵ As with HIT's primary use, secondary uses have the potential to dramatically improve public health.¹⁵⁶ As Bryan Sivak, chief technology officer at the Department of Health and Human Services ("HHS"), stated in November 2012, "data, open data, has the power to fundamentally change health care in this country."¹⁵⁷

Unfortunately, for a variety of reasons, effective HIE systems have been slow to develop. Privacy concerns present a barrier to HIE since providers are concerned about liability for

¹⁵² Charles Safran et al., *Toward a National Framework for the Secondary Use of Health Data: An American Medical Informatics Association White Paper*, 14 J. AM. MED. INFORMATICS ASS'N 1 (2007).

¹⁵³ HEALTH INFO. & QUALITY AUTH., INTERNATIONAL REVIEW OF SECONDARY USE OF PERSONAL HEALTH INFORMATION 13 (2012), available at <http://www.hiqa.ie/publications/international-review-secondary-use-personal-health-information>.

¹⁵⁴ Epidemiology is the branch of medicine that deals with disease incidence, distribution, and control. Its essential role is to improve public health. See generally R. BONITA ET AL., WORLD HEALTH ORG., BASIC EPIDEMIOLOGY (2d ed. 2006), available at http://whqlibdoc.who.int/publications/2006/9241547073_eng.pdf.

¹⁵⁵ HEALTH INFO. & QUALITY AUTH., *supra* note 153, at 13–14.

¹⁵⁶ *Id.*

¹⁵⁷ Alex Ruoff, *Claims Administration: HHS Aims to Leverage Health Data to Spur Innovation in Private, Public Sector*, MEDICARE REP., Nov. 30, 2012 (internal quotation marks omitted), available at Bloomberg BNA: Health Law Res. Ctr., 23 MCR 1410.

inappropriately sharing protected health information (“PHI”).¹⁵⁸ Such liability arises under the Health Insurance Portability and Accountability Act of 1996 (“HIPAA”), which established a regulatory framework for maintaining privacy and security of an individual’s identifiable health information.¹⁵⁹ Providers also face liability under state laws and under common law causes of action.¹⁶⁰ Interoperability problems between HIT systems have also impeded HIE, because, as a rule, HIT manufacturers have not had an incentive to design HIT systems to communicate with one another. On the contrary, HIT manufacturers and providers have had incentives to prevent HIE, due to manufacturer concerns about protecting their intellectual property and provider concerns about data privacy.¹⁶¹ This market failure has prompted the federal government to intervene on several occasions.¹⁶²

¹⁵⁸ HIPAA defines PHI as “identifiable health information that is transmitted or maintained in any form or medium . . . , but excludes certain educational records and employment records.” Ctrs. for Disease Control & Prevention, *HIPAA Privacy Rule and Public Health: Guidance from CDC and the U.S. Department of Health and Human Services*, 52 MORBIDITY & MORTALITY WKLY. REP. 1, 1 (Supp. May 2, 2003).

¹⁵⁹ Title II of HIPAA requires HHS to promulgate rules and standards for using and sharing health care information. These requirements only apply to “covered entities,” which includes all providers transmitting any information in an electronic form in connection with a transaction for which HHS has adopted a standard, as well as health insurance companies and health-care clearinghouses. 45 C.F.R. § 160.103 (2012); *For Covered Entities and Business Associates*, U.S. DEP’T OF HEALTH & HUMAN SERVS., <http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/index.html> (last visited Aug. 24, 2013).

¹⁶⁰ See, e.g., *Doe v. Marselle*, 675 A.2d 835 (Conn. 1996) (discussing a state law prohibiting disclosure of HIV testing information).

¹⁶¹ The market for HIT services is a competitive one, although relatively few vendors have considerable market power. Anthony Guerra, *Five Vendors Dominate HIE Market*, INFO. WK. (July 8, 2010, 8:00 AM), <http://www.informationweek.com/healthcare/clinical-systems/five-vendors-dominate-hie-market/225702631> (reporting on KLAS, HEALTH INFORMATION EXCHANGES: PERCEPTION IN AN EXPANDING FRONTIER (2010)).

¹⁶² Promoting the effective use of HIT and HIE has been one of the rare issues to receive bipartisan support. David J. Brailer, *Presidential Leadership and Health Information Technology*, 28 HEALTH AFF. w392 (2009), available at <http://content.healthaffairs.org/content/28/2/w392.full>.

2. *THE GOVERNMENT STEPS IN: THE HITECH ACT AND THE AFFORDABLE
CARE ACT*

The Health Information Technology for Economic and Clinical Health Act (“HITECH Act”)¹⁶³ and the Patient Protection and Affordable Care Act (“ACA”) are the most important federal initiatives in HIT and HIE. First, the HITECH Act is designed to accelerate providers’ EMR adoption and to incentivize national health care HIT infrastructure creation. It commits between \$14 billion and \$27 billion in federal funding to establish a nationwide health information network.¹⁶⁴ Individual doctors can receive between \$44,000 and \$63,000 over the course of the program, and payments to hospitals begin at \$2 million.¹⁶⁵ The HITECH Act also changes Medicare and Medicaid reimbursement rates to incentivize HIT adoption. For example, if a hospital fails to implement an EMR system by 2015, it will receive reduced payments under Medicare fee-for-service.¹⁶⁶ In addition, the HITECH Act establishes programs within the ONC to guide physicians, hospitals, and other key entities to adopt EMR and achieve meaningful use.¹⁶⁷ Finally, because the HITECH Act anticipates a major increase in HIE, it widens the scope of privacy and security protections available under HIPAA, increases liability for non-compliance, and provides for greater enforcement.¹⁶⁸

¹⁶³ President Obama signed the HITECH Act into law in 2009 as part of the American Recovery and Reinvestment Act (“ARRA,” also known as the stimulus bill). American Recovery and Reinvestment Act of 2009, Pub. L. No. 111-5, 123 Stat 115.

¹⁶⁴ Medicare and Medicaid Programs; Electronic Health Record Incentive Program, 75 Fed. Reg. 1844, 1973 (to be proposed Jan. 13, 2010) (to be codified at 42 C.F.R. pts. 412, 413, 422 & 495).

¹⁶⁵ David Blumenthal, *Launching HITECH*, 362 NEW ENG. J. MED. 382, 384 (2010).

¹⁶⁶ *See id.* at 382–84.

¹⁶⁷ Medicare and Medicaid Programs; Electronic Health Record Incentive Program, 75 Fed. Reg. 44,313, 44,317 (July 28, 2010) (to be codified at 42 C.F.R. pts. 412, 413, 422, & 495).

¹⁶⁸ *Health Information Privacy: HITECH Act Enforcement Interim Final Rule*, U.S. DEP’T OF HEALTH & HUMAN SERVS., <http://www.hhs.gov/ocr/privacy/hipaa/administrative/enforcementrule/hitechenforcementiffr.html>

The ACA also promotes HIT.¹⁶⁹ For example, the ACA established the Center for Medicare and Medicaid Innovation, which has implemented projects that require an information technology infrastructure to coordinate care. This includes requiring medical home demonstration projects in federally qualified health centers to utilize electronic record keeping for communicating with patients and for prescribing.¹⁷⁰

3. *ESTABLISHING HEALTH INFORMATION EXCHANGES*

In addition to incentivizing HIT, the HITECH Act and the ACA help establish state and federal health information exchanges, which promote health data transfer. The HITECH Act provided the states with federal grants of more than \$560 million to establish statewide HIEs.¹⁷¹ Under this system, each state is responsible for working independently to establish its own exchange. The ONC is responsible for governing the program through its administration of federal grants,¹⁷² and states are required to adopt a transparent stakeholder process for

(last visited Aug. 23, 2013).

¹⁶⁹ For a discussion of the major components of ACA, see Ryan Abbott, *Treating the Health Care Crisis: Complementary and Alternative Medicine for PPACA*, 14 DEPAUL J. HEALTH CARE L. 35 (2011).

¹⁷⁰ Buntin et al., *supra* note 143, at 464–65.

¹⁷¹ Blumenthal, *supra* note 165, at 384. This raises the issue of sustainability. At present, only a small portion of HIEs, 10%, have revenues that exceed operating expenses and investment capital. Alex Ruoff, *Information Exchange: Future of Health Information Exchange Promising but Uncertain, Experts Tell ONC*, HEALTH IT L. & INDUSTRY REP., Feb. 4, 2013, *available at* Bloomberg BNA: Health Law Res. Ctr., 5 HITR 5. Unless this trend changes, there will need to be continued public subsidies for HIEs.

¹⁷² The ONC awards grants to States, eligible territories, and qualified State-designated entities through programs such as the State HIE Cooperative Agreement Program. *HITECH Programs & Advisory Committees: State Health Information Exchange*, HEALTHIT.GOV (last visited Aug. 23, 2013), <http://www.healthit.gov/policy-researchers-implementers/state-health-information-exchange>. Both the HITECH Act and the ACA makes funding available for this program. For example, in January 2011, “an additional \$16 million was made available to states through ONC’s new Challenge Grants program. This program . . . provide[s] funding to states to encourage breakthrough innovations for [HIE] that can be leveraged [nationally].” *Id.*

developing HIEs.¹⁷³ States, as opposed to the federal government, are well situated to oversee these exchanges' development, since they are the custodians of Medicaid and public health data.¹⁷⁴ On the other hand, interoperability is already one of the most significant problems confronting HIEs, and having 50 individually designed HIEs may create barriers to interstate information transfer.¹⁷⁵ The ONC is well aware of this interoperability dilemma, and is working to promote a set of standards, services, and policies that will facilitate HIE through its Nationwide Health Information Network.¹⁷⁶ These services include the promotion of free open-source software supporting HIE.¹⁷⁷ These federal initiatives have successfully stimulated HIE development; there are currently over 200 public or private HIEs working on intrastate or interstate levels.¹⁷⁸ Over 70 of these are already operational, and they are transmitting data used by health care stakeholders.¹⁷⁹ The ONC has also supported the development of a national HIE—the eHealth Exchange.¹⁸⁰

¹⁷³ 42 U.S.C. § 18031 (Supp. IV 2010).

¹⁷⁴ Blumenthal, *supra* note 165, at 384–85.

¹⁷⁵ See generally Arthur L. Kellermann & Spencer S. Jones, *What It Will Take to Achieve the As-Yet-Unfulfilled Promises of Health Information Technology*, 32 HEALTH AFF. 63, 66 (2013).

¹⁷⁶ Blumenthal, *supra* note 165, at 385.

¹⁷⁷ CONNECT is open-source software that supports HIE locally and nationally. It uses Nationwide Health Information Network standards to make sure HIEs are compatible with one another. Although the software was initially developed for use by federal agencies, it is now available to any organization free of charge. *Federal Health Architecture: CONNECT: A Gateway to the Nationwide Health Information Network*, HEALTHIT.GOV <http://www.healthit.gov/policy-researchers-implementers/connect-gateway-nationwide-health-information-network#node-575> (last visited Aug. 23, 2013).

¹⁷⁸ EHEALTH INITIATIVE, THE STATE OF HEALTH INFORMATION EXCHANGE IN 2010: CONNECTING THE NATION TO ACHIEVE MEANINGFUL USE 5–8 (2010), *available at* <http://ihealthtran.com/pdf/eHI%20-%20HIE%20Final%20Report.pdf>.

¹⁷⁹ *Id.* at 8 (noting that this number is up from 9 in 2004, 32 in 2007, and 57 in 2009).

¹⁸⁰ The eHealth Exchange was formerly called the Nationwide Health Information Network (“NwHIN”) Exchange. *Exchange of Health Information: Standards & Interoperability*, HEALTHIT.GOV (last visited Aug. 23, 2013), <http://www.healthit.gov/policy-researchers-implementers/strategic-plan-progress-report/standards-interoperability>. When it was the NwHIN

II. THE FDA, PRODUCT SPONSORS, AND THIRD PARTIES

A. USING HIES TO POWER PHARMACOVIGILANCE

Part I's analysis suggests that HIEs may play a vital role in post-market drug safety risk assessment, since observational data mining is already a core, if underutilized, component of pharmacovigilance and since the aggregated HIE data would be superior to existing databases. The HIE datasets' relatively large size would permit greater statistical analysis accuracy and the ability to detect less rare events than is currently possible with smaller datasets. HIEs should also minimize problems associated with bias and selectivity. Voluntary databases, like FAERS, require health care providers to recognize and report an association between a drug and an adverse effect, and these databases likely suffer from underreporting.¹⁸¹ HIEs, on the other hand, may automatically include this information. Unlike HIEs, other large databases, such as those used with Medicaid, do not represent the entire population.¹⁸² Finally, HIEs will presumably contain a large number of data fields, such as for drug use, symptoms, diagnoses, and laboratory data. With more extensive data available, researchers can generate new diagnoses or adverse event hypotheses that are not limited to existing diagnoses.¹⁸³

However, for HIEs to achieve their potential, appropriate data has to be collected and made accessible to stakeholders in the pharmacovigilance process. This, in turn, requires resolution of a number of challenges. The FDA has already issued guidelines to specify what

exchange, it was funded and operated entirely by the ONC. *Id.* Now, ONC has turned over control of the eHealth Exchange to a public-private partnership, Healthway. *Id.* Starting in 2013, users of the exchange will have to pay to use the service. Alex Ruoff, *Information Exchange: Users of eHealth Exchange to Begin Paying for Network Services in 2013*, HEALTH CARE POL'Y REP., Oct. 29, 2012, available at Bloomberg BNA: Health Law Res. Ctr., 20 HCPR 1700.

¹⁸¹ Wilson, *supra* note 82, at 130 tbl. 2.

¹⁸² *Id.* at 130.

¹⁸³ *Id.* at 130–31.

kinds of data are useful for pharmacovigilance.¹⁸⁴ Stakeholders in the HIEs implementation process will need to take this into account when they design data collection systems. Although HIEs designed without secondary uses in mind may still be helpful, they will be more useful if efforts are made to acquire sufficient and accurate data about drug use. Failure to design HIEs with an eye toward pharmacovigilance may mean that the data will have limited utility. In addition to collecting the right kinds of data, to facilitate pharmacovigilance the data in multiple HIEs should be susceptible to aggregation. Centralized standard setting and interoperability requirements can help to ensure aggregation, which would allow efficient analysis of data in HIEs.¹⁸⁵ If information exchange is restricted to individual HIEs, or is not efficiently searchable, it renders meta-analysis far more challenging.

Privacy is another major, and longstanding, issue with HIE use. Health information is highly personal, and patients remain concerned that EMRs are not secure.¹⁸⁶ These privacy concerns have led to various HIE patient participation models, which will impact data mining. In a no-consent model, HIEs are free to exchange information without patient consent.¹⁸⁷ Other models allow patients to either opt-in¹⁸⁸ or opt-out¹⁸⁹ of all information exchange, while more

¹⁸⁴ *E.g.*, GUIDANCE FOR INDUSTRY, *supra* note 39, at 4–5.

¹⁸⁵ See Kendra Casey Plank, *Interoperability: Consistent Standards the Missing Link in Health Data Exchange*, Panelists Say, HEALTH IT L. & INDUSTRY REP., Dec. 3, 2012, available at Bloomberg BNA: Health Law Res. Ctr., 4 HITR 9 (noting that industry might be on the right path to interoperability, but that it is years away). Consistent national exchange standards will be key to true interoperability.

¹⁸⁶ See, *e.g.*, DARRELL M. WEST & ALLAN FRIEDMAN, BROOKINGS INST., HEALTH INFORMATION EXCHANGES AND MEGACHANGE 4 (2012), available at http://www.brookings.edu/~media/research/files/papers/2012/2/08%20health%20info%20exchange%20friedman%20west/0208_health_info_exchange_west.pdf.

¹⁸⁷ Sarah R. Rupp, *Making Room for Patient Autonomy in Health Information Exchange: The Role of Informed Consent*, 56 ST. LOUIS U. L.J. 885, 890 (2012).

¹⁸⁸ See Howard Anderson, *Survey: 'Opt-In' for HIE Consent Is Rare*, HEALTHCAREINFOSECURITY.COM (July 23, 2010),

sophisticated systems allow patients to opt-in or opt-out with respect to certain types of information.¹⁹⁰ If patients or other stakeholders restrict the amount of information available due to privacy concerns or other considerations, the restriction will result in less information available for epidemiological study. Therefore, a no-consent model will be most useful for pharmacovigilance, since it is the participation model most likely to produce the largest and least-biased amount of information.¹⁹¹ However, the downside is that the no-consent model does not accommodate individual choice and increases the risk of privacy loss. Even so, HIPAA permits the no-consent model.¹⁹²

One way to better protect patient confidentiality while still permitting broad access to HIE information is to de-identify patient data. This means that HIEs, or aggregated data from HIEs, would only contain clinical information that is not associated with any identifiable patient characteristic (like a name or a social security number). The database would be anonymous.¹⁹³

http://www.healthcareinfosecurity.com/articles.php?art_id=2779 (explaining that an “Opt-In” model would create an administrative burden by requiring every patient to sign a consent form).

¹⁸⁹ MELISSA M. GOLDSTEIN & ALISON L. REIN, CONSUMER CONSENT OPTIONS FOR ELECTRONIC HEALTH INFORMATION EXCHANGE: POLICY CONSIDERATIONS AND ANALYSIS ES-1, 5–7 (2010), *available at* <http://www.healthit.gov/sites/default/files/choicemodelfinal032610.pdf>. For example, the Delaware HIE uses an opt-out consent mechanism for provider access (but requires no consent for EMR creation), and Maryland, Kentucky, and Nebraska all use an opt-out approach. *Id.* at A-1, A-3; MO. OFFICE OF HEALTH INFO. TECH., HEALTH INFORMATION EXCHANGE OPERATIONAL PLAN L-1 (2010), *available at* http://www.dss.mo.gov/hie/action/pdf2010/operationalplan_draft.pdf.

¹⁹⁰ For example, patients may discriminate as to information based on data type, provider, time range, or purpose. GOLDSTEIN & REIN, *supra* note 189, at ES-1, 5–7.

¹⁹¹ *See* OFFICE FOR CIVIL RIGHTS, GUIDANCE REGARDING METHODS FOR DE-IDENTIFICATION OF PROTECTED HEALTH INFORMATION IN ACCORDANCE WITH THE HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA) PRIVACY RULE 5–8 (2012), *available at* http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/De-identification/hhs_deid_guidance.pdf (noting that preserving as much data as possible in de-identification efforts maintains the usefulness of information).

¹⁹² GOLDSTEIN & REIN, *supra* note 189, at 2.

¹⁹³ De-identification is difficult in the best of situations. Even lacking overt identifying

Alternatively, a database that protects patient confidentiality could have a dual structure, with a primary and a secondary version. The primary version of the HIE would contain identifiable patient data, but with limited access. The primary version would only be used for direct patient care (meaning a health care provider would use it to look up a specific patient's data). The secondary version would redact all identifying information, would permit broader access, and could be used for secondary purposes (such as pharmacovigilance). If data is de-identified, it is not within HIPAA's scope and is open to dissemination without restriction¹⁹⁴ because HIPAA assumes that de-identified data ensures complete anonymity.¹⁹⁵ While it may be possible to re-identify data,¹⁹⁶ civil and criminal penalties for misusing protected data can minimize that risk. HIPAA is not the only statute that protects patient privacy; a complex network of federal and state statutes and common law rights protect privacy, and a variety of government and private actors are responsible for enforcement.¹⁹⁷ The HIE datasets' immense size may also make it more difficult to identify individual patients.

information such as names and social security numbers, it may still be possible to identify individual patients with available information, or to re-identify data through various procedures. C. Christine Porter, *De-identified Data and Third Party Data Mining: The Risk of Re-Identification of Personal Information*, 5 SHIDLER J.L. COM. & TECH. 3 (2008), available at http://digital.law.washington.edu/dspace-law/bitstream/handle/1773.1/417/vol5_no1_art3.pdf. Also, there is always the risk that those in charge of de-identification will simply fail to do so.

¹⁹⁴ See Robert Gellman, *The Deidentification Dilemma: A Legislative and Contractual Proposal*, 21 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 33, 38 (2010) (noting HIPAA's assumption that de-identified data ensures complete anonymity).

¹⁹⁵ The HIPAA Privacy Rule requires seventeen specific fields of data to be removed or generalized for protected health information ("PHI") to be considered de-identified. *Id.* It also requires there be no "actual knowledge that the information could be used alone or in combination with other information to identify an individual." 45 C.F.R. § 164.514(b)(2)(ii) (2012).

¹⁹⁶ Gellman, *supra* note 194, at 34–35, 39.

¹⁹⁷ See KRISTEN ROSATI ET AL., AN ANALYSIS OF LEGAL ISSUES RELATED TO THE USE OF ELECTRONIC HEALTH INFORMATION IN PHARMACOVIGILANCE PROGRAMS 2–8 (2008), available at <http://www.brookings.edu/~media/events/2008/6/13-drug-safety/rosati--ehi-drug-safety-collaboration-legal-guidance-developed-by-coppersmith-gordon-04-15-08>.

HIEs' privacy concerns exist in other contexts. For instance, statewide prescription drug monitoring programs ("PDMP") maintain centralized databases with information on every prescription written for controlled substances within the state.¹⁹⁸ This permits approved health care providers to check online and determine which controlled substances a patient is receiving. These databases are very useful in clinical practice since they allow physicians to determine whether a patient is shopping around to receive multiple prescriptions for substances susceptible to abuse. Federal and state regulatory and law enforcement agencies also monitor aggregated data to determine whether controlled substances are being diverted. As with HIEs, the federal government subsidizes PDMP establishment with consistent national criteria and promotes information exchange.¹⁹⁹ Just like HIEs, PDMPs have privacy concerns because they contain highly confidential data on a sizable portion of the state's population and a relatively large number of providers have access to this data. But even if access were more tightly restricted, no electronic system is immune to breach—no matter how effective its security.²⁰⁰ Notwithstanding these privacy concerns, the HITECH Act and the ACA mandate HIE creation, and HIEs have great potential public health and efficiency benefits. To further safeguard privacy, aggregated

¹⁹⁸ See OFFICE OF NAT'L DRUG CONTROL POLICY, PRESCRIPTION DRUG MONITORING PROGRAMS (2011), *available at* <https://www.ncjrs.gov/pdffiles1/ondcp/pdmp.pdf>.

¹⁹⁹ The National All Schedules Prescription Electronic Reporting Act ("NASPER"), enacted in 2005, is facilitating PDMP establishment. National All Schedules Prescription Electronic Reporting Act of 2005, Pub. L. No. 109-60, 119 Stat. 1979. The Act created a U.S. Department of Health and Human Services grant program for states to implement or enhance prescription drug monitoring programs. *Id.* § 3.

²⁰⁰ PDMPs have already been illegally accessed in a number of high profile incidents. For example, in 2009, hackers broke into a Virginia state PDMP, deleted over 8 million patients' records, "and replaced the site's homepage with a ransom note demanding \$10 million for the return of the records." Brian Krebs, *Hackers Break into Virginia Health Professions Database, Demand Ransom*, WASH. POST (May 4, 2009, 6:39 PM), http://voices.washingtonpost.com/securityfix/2009/05/hackers_break_into_virginia_he.html.

data for HIE secondary use should only be collected in a de-identified manner,²⁰¹ re-identifying this data should be prohibited.

B. GOVERNMENT AGENCIES

The next major implementation question that using HIEs for pharmacovigilance poses: Who should have access to aggregated HIEs data? Should it be government agencies, product sponsors, and/or third parties? The answer to this question will have substantial implications for a new pharmacovigilance system.

The first option is to restrict access to aggregated HIE data to government agencies. The principal government agency would be the FDA, which could use this data for analysis in more or less the same way it currently analyzes FAERS and the Sentinel System. The FDA is not the only government agency that could use this data for pharmacovigilance. For example, researchers at the National Institutes of Health (“NIH”) routinely study approved drugs’ safety and efficacy, and access to this data would improve their research.²⁰² Other agencies like the National Science Foundation (“NSF”) conduct similar activities.²⁰³

Government agencies should be first in line for access to HIE data for pharmacovigilance. Government agencies may be the least likely to abuse this data given the

²⁰¹ HHS Office for Civil Rights (“OCR”) has released guidance on de-identifying PHI. It does note that even when properly de-identified, there is a very small risk de-identified data can be linked back to individual patients, and there is no fail-safe method to prevent this. OFFICE FOR CIVIL RIGHTS, *supra* note 191, at 10–22.

²⁰² NIH, part of HHS, is the nation’s leading medical research agency. *About NIH*, NAT’L INSTS. OF HEALTH, <http://www.nih.gov/about/> (last updated June 6, 2013). In 2011, 10% of NIH’s approximately \$30.9 billion budget went toward intramural research. *About NIH: NIH Budget*, NAT’L INSTS. OF HEALTH, <http://www.nih.gov/about/budget.htm> (last updated Sept. 18, 2012). Some 6000 scientists work in NIH’s own laboratories, many of whom investigate the safety and efficacy of approved drugs as part of their mission to improve public health. *About NIH*, *supra*.

²⁰³ *About the National Science Foundation*, NAT’L SCI. FOUND., <http://www.nsf.gov/about/> (last visited Aug. 20, 2013).

agencies' missions to serve the public, and given the various legal constraints placed on federal and state employees.

C. *PRODUCT SPONSORS*

Permitting pharmaceutical manufacturers access to HIEs' data may be beneficial because, in some respects, pharmaceutical manufacturers are the ideal pharmacovigilance monitors. They have detailed knowledge about their own products, extensive technical expertise, and may have resources beyond, or complementary to, the FDA's resources. In the current system, pharmaceutical manufacturers are already the parties most closely monitoring product performance, both because the FDA may require them to do so and because they may face liability for failing to act after becoming aware (or after they should have become aware) of safety issues.²⁰⁴ Access to a larger patient dataset would permit manufacturers to conduct improved observational research.

However, it is problematic to make product sponsors the main parties responsible for pharmacovigilance because of their pecuniary incentive to suppress data unfavorable to their products. Even a cursory examination of recent judgments against pharmaceutical manufacturers shows that financial incentives are a powerful determinant of behavior. For example, in July 2012, GlaxoSmithKline ("GSK") pled guilty and paid \$3 billion to resolve criminal and civil liability arising from the company's unlawful prescription drug promotion, failure to report safety data, and false price reporting practices.²⁰⁵ Currently, this remains "the largest health care

²⁰⁴ See JUDITH A. JOHNSON, CONG. RESEARCH SERV., R42130, FDA REGULATION OF MEDICAL DEVICES 15–17 (2012), available at <http://www.fas.org/sgp/crs/misc/R42130.pdf>.

²⁰⁵ *GlaxoSmithKline to Plead Guilty and Pay \$3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data*, U.S. DEP'T OF JUSTICE (July 2, 2012), <http://www.justice.gov/opa/pr/2012/July/12-civ-842.html>.

fraud settlement in U.S. history and the largest payment ever by a drug company.”²⁰⁶

There is always the possibility that product sponsors would attempt to use the additional data to support misleading statements. However, manufacturers are still an indispensable component of the pharmacovigilance system, and they do remove products from the market on their own initiative.²⁰⁷ Drug companies tend to be the first party to detect and prove causal connections between drugs and adverse events, either due to liability concerns or due to companies functioning as the system intended.

Product sponsors might conceivably use HIE data to undermine competitors. However, there is reason to doubt this will happen given that companies do not seem to currently devote significant resources to attacking rival drugs. In terms of clinical research, the reasons for this are clear enough: clinical trials are very expensive, and head-to-head trials can be extremely risky even for sponsors that are influencing study design.²⁰⁸ It is less clear why firms do not appear to

²⁰⁶ *Id.*

²⁰⁷ *Drug Recalls*, FDA, <http://www.fda.gov/Drugs/DrugSafety/DrugRecalls/default.htm> (last updated Aug. 29, 2013).

²⁰⁸ For example, AstraZeneca funded the SATURN trial to prove its top-selling drug Crestor worked better than Lipitor. See Stephen J. Nicholls et al., *Effect of Two Intensive Statin Regimens on Progression of Coronary Disease*, 365 NEW ENG. J. MED. 2078 (2011). Pfizer’s patent on Lipitor was due to expire in November 2011, and AstraZeneca feared that patients with high cholesterol would be switched en masse from both drugs to a less expensive, generic version of Lipitor. See *id.* However, after following 1,039 high-risk patients for two years, the study showed no significant difference between the two drugs. *Id.* Years before this in 2003, Bristol-Myers Squibb (“BMS”) had funded the “Prove-It” study to compare its statin Pravachol head-to-head with Lipitor. See Christopher P. Cannon et al., *Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes*, 350 NEW ENG. J. MED. 1495 (2004). The study was designed to minimize risk to BMS. See *id.* First, it was a “noninferiority trial,” so Pravachol only needed to hold its own against Lipitor. *Id.* at 1495. Second, the follow-up ended at 2 years, which was the point at which most experts believed differences between the drugs would approach measurability. See *id.* at 1500–03. In the end, this strategy backfired when the study ended up showing that Lipitor patients had a 16% lower risk of heart attack after a mere 30 days. *Id.* at 1499.

have engaged in data mining solely to discredit rival drugs.²⁰⁹ The industry may have recognized that over the long-term this sort of research is detrimental to pharmaceutical companies collectively.

In any event, the solution to the incentive problem is not to eliminate product sponsors' role in the regulatory process any more than the FDA should be replaced. What is needed to improve the system is not an *alternative* party to conduct regulation, but a *complementary* party.

D. *THIRD PARTIES*

Third parties in the pharmacovigilance system are a diverse group. A variety of actors already play a role: academic researchers, patient advocate groups, trade associations, and non-profits, to name a few. Academics, for a number of reasons, conduct and publish research that the FDA uses to evaluate drug risk–benefit profiles. Unfortunately, some of these researchers, perhaps a troublingly large number, have industry connections with a corresponding incentive to publish industry-friendly research. Others are sponsored by non-industry sources: the government, universities, or non-profits (e.g., the Gates Foundation).²¹⁰ These academics have their own incentives for conducting research, such as to promote their reputations within the academic community and to attract grant funding. As a group, they do not have an obvious incentive to publish either pro- or anti-industry data. Their funding may simply be provided to benefit the public without a direct financial interest in the outcome. Not everyone is motivated solely by financial considerations, and third parties can have a variety of non-financial incentives

²⁰⁹ Pharmaceutical manufacturers do engage in data mining to craft individualized sales messages for specific doctors and to promote their products over competitor products at the individual physical level. *See, e.g.,* *IMS Health Inc. v. Ayotte*, 490 F. Supp. 2d 163, 167–70 (D.N.H. 2007) (providing background information on the practice of detailing), *vacated*, 550 F.3d 42 (1st Cir. 2008), *abrogated by* *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011).

²¹⁰ Over 80% of the NIH's budget funds over 300,000 scientists at over 2500 universities and research institutions. *About NIH*, *supra* note 202.

to act.²¹¹

This may suggest that academic researchers do not need an additional financial incentive to use HIEs for pharmacovigilance. However, as the Vioxx case shows, academics may not do enough to assist regulators without additional incentives. Currently, academics studying adverse effects are motivated to submit their research to scientific journals, which in turn make the information available to the public after a lengthy publication process. Yearlong delays in publishing are not uncommon. It would be more beneficial if academics would submit information directly to the FDA. Also, academics should translate their research into a format regulators can utilize. Some bridge is necessary to convert published studies into an FDA determination. Put another way, pharmacovigilance requires engineers and not just theoretical physicists.

Third parties with industry-adverse interests also play a role in pharmacovigilance. For instance, law firms and potential litigants stand to gain if an approved drug is found to be unsafe since pharmaceutical manufacturers have tort liability on grounds ranging from publication of

²¹¹ This is evident, for example, in the free and open-source software movements, in which programmers offer their services to develop software that is made available to the public free of charge. The free software movement largely came about due to the efforts of Richard Stallman, who founded the Free Software Foundation in 1985. *Meet the Founder, Staff and Board of Directors of the Free Software Foundation*, FREE SOFTWARE FOUND., <http://www.fsf.org/about/staff-and-board> (last visited Aug. 23, 2013). Stallman advocates for free software and access to source code. José J. González de Alaiza Cardona, *Open Source, Free Software, and Contractual Issues*, 15 TEX. INTELL. PROP. L.J. 157, 167–69 (2007). Together with others, he helped to create and disseminate the Linux operating system. *Id.* Programmers have a mixture of reasons for participating in these efforts: they may have financial motivations that are not directly tied to the specific active programming (e.g., commercializing ancillary services), they may have philosophical objections to proprietary software, or they may simply be motivated by altruism. Josh Lerner & Jean Tirole, *The Open Source Movement: Key Research Questions*, 45 EUROPEAN ECON. REV. 819, 822–23 (2001); cf. Richard E. Fontana, *Open Source License Enforcement and Compliance*, in OPEN SOURCE AND FREE SOFTWARE 2009: BENEFITS, RISKS AND CHALLENGES IN TODAY'S ECONOMIC ENVIRONMENT 77 (PLI Intellectual Property, Course Handbook Ser. No. G-989, 2009) (discussing, for example, the Red Hat business model).

misleading advertisements to the sale of dangerous products.²¹² An injured patient may claim that a drug was defectively designed or manufactured, or that there was a failure to warn customers about dangers associated with a drug.²¹³ In addition, plaintiffs may bring negligence- and fraud-based claims, such as for negligent and fraudulent misrepresentation.²¹⁴ Finally, plaintiffs may bring warranty claims, both expressed and implied, as well as statutory causes of action relating to unfair and deceptive trade practices.²¹⁵ In such actions, an important consideration is whether the manufacturer had clean hands regarding its scientific performance and the presentation of data to the FDA.²¹⁶ Companies have historically preferred to settle cases rather than see information relating to their misdeeds become public knowledge.²¹⁷

HIE access will improve tort litigation for plaintiffs' attorneys, who play a valuable role in drug regulation that compliments the FDA.²¹⁸ Civil litigation helps ensure that compensation for injury is paid, and the threat of liability motivates manufacturers to comply with FDA regulations, which creates a valuable deterrent preventing injury *ex ante*.²¹⁹

Yet the Vioxx case illustrates why tort liability alone fails to produce the right public health outcomes. Similar to the academic process, the tort system moves slowly; Merck did not

²¹² Tort cases in which a plaintiff seeks damages for lack of efficacy are very rare. ABBOTT & DUKES, *supra* note 113, at 193, 199.

²¹³ *Id.* at 194.

²¹⁴ *Id.* at 194–95.

²¹⁵ *Id.*

²¹⁶ *Id.* at 197.

²¹⁷ *Id.*

²¹⁸ JOHN BRAITHWAITE, CORPORATE CRIME IN THE PHARMACEUTICAL INDUSTRY 346 (1984) (“In most countries, but especially the United States, product liability law rather than criminal law has provided most of the deterrence against corporate crime in the pharmaceutical industry. Compensation, not deterrence, is the recognized function of product liability law. Yet the conclusion from my interviews was that pharmaceutical executives report fear of product-liability suits as a reason for obeying the Food, Drug and Cosmetic Act of immensely greater importance than fear of criminal prosecution or any other regulatory action.”).

²¹⁹ ABBOTT & DUKES, *supra* note 113, at 208.

begin to face significant liability until long after the risk of Vioxx was known. This may be because plaintiffs' attorneys are primarily motivated to recover for their client's damages rather than to prevent future injuries. As such, plaintiffs' attorneys may have an incentive to delay suing and accumulate additional damages or cases, or to allow other attorneys to take the risk of litigating complex issues. Moreover, the results of litigation may never become public knowledge. Very few cases are now concluded at trial, and manufacturers routinely insist on confidentiality agreements as a standard feature of settlements.²²⁰ While in the long run tort liability might produce the right economic result, this occurs at great human cost.

The issue of tort liability is politically charged with powerful lobbies on both sides. Critics of tort liability argue that legal system abuses increase market costs and punish innocent manufacturers.²²¹ They argue that plaintiffs file frivolous claims, and damage awards are grossly disproportionate to alleged harms.²²² On this basis, a number of states have proscribed litigation against a manufacturer in connection with a drug that has received FDA approval.²²³ For example, in Texas, "unless the [FDA] explicitly determine[s] that a pharmaceutical manufacturer committed fraud . . . Texas residents [cannot] pursue a 'failure-to-warn' claim."²²⁴ Historically, the FDA has acknowledged that state tort claims are important for drug regulation, but the

²²⁰ See John H. Langbein, *The Disappearance of Civil Trial in the United States*, 122 YALE L.J. 522, 524 (2012) (noting that the proportion of civil cases concluded at trial is now below 2% in the federal courts and below 1% in state courts).

²²¹ Mark Herrmann, *Why the Texas Vioxx Decision Matters*, DRUG & DEVICE L. BLOG (Apr. 22, 2007, 10:57 AM), <http://druganddevicelaw.blogspot.com/2007/04/why-texas-vioxx-decision-matters.html>. See generally DANIEL E. TROY, STATE-LEVEL PROTECTION FOR GOOD-FAITH PHARMACEUTICAL MANUFACTURERS (2006), available at https://www.fed-soc.org/doclib/20070403_DanTroyProtectionforPharms.pdf.

²²² Paul H. Rubin & Joanna M. Shepherd, *Tort Reform and Accidental Deaths*, 50 J.L. & ECON. 221, 223 (2007).

²²³ Russell G. Thornton, *Preemption, Tort Reform, and Pharmaceutical Claims*, 20 BAYLOR U. MED. CENTER PROC. 418 (2007).

²²⁴ *Id.* at 418.

agency abruptly changed its position in 2006 and now supports federal preemption of state court claims.²²⁵ For states that have not statutorily limited tort liability, however, the Supreme Court rejected preemption of state tort mislabeling claims in *Wyeth v. Levine*.²²⁶

In addition to potential litigants, health care insurers may be interested in sponsoring research on drug risk–benefit profiles to avoid paying for ineffective or unsafe therapies. The problem here may be that insurers do not have incentives to share the results of their research. For example, multiple insurers had independently restricted access to Vioxx prior to its withdrawal, some on the basis of their independent research, but this information was not effectively disseminated.²²⁷

There is another way that third parties are currently involved in pharmacovigilance; the FDA allows third parties to express safety, scientific, or legal concerns regarding a product with a citizen petition.²²⁸ Any “interested person” may file a petition to request that the FDA “issue, amend, or revoke a regulation or order or take or refrain from taking any other form of administrative action.”²²⁹ These petitions are filed by three groups: (1) brand firms, which file to request denial of a generic’s Abbreviated New Drug Application (“ANDA”);²³⁰ (2) generics

²²⁵ *Wyeth v. Levine*, 555 U.S. 555, 557–81 (2009).

²²⁶ *Id.* Congress has expressly preempted common law causes of action for certain medical devices. *See Riegel v. Medtronic, Inc.*, 552 U.S. 312, 321–25 (2008) (discussing 21 U.S.C. § 360k).

²²⁷ *Some Insurers Limited Vioxx*, USA TODAY (Oct. 4, 2004, 12:09 AM), http://usatoday30.usatoday.com/money/industries/health/drugs/2004-10-04-vioxx-insurers_x.htm.

²²⁸ 21 C.F.R. § 10.30 (2012).

²²⁹ *Id.* § 10.30(b).

²³⁰ An ANDA is an application from a generics company to the FDA to approve a generic drug product. After approved, an applicant may manufacture and market the generic drug. *Abbreviated New Drug Application (ANDA): Generics*, FDA, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/> (July 17, 2013).

companies, which file, for example, to obtain FDA approval to submit an ANDA; and (3) “other parties, such as universities, doctors, and hospitals,” which file to raise safety concerns or to obtain industry guidelines.²³¹

In practice, brand companies—seeking to delay or to prevent generic competition—are the primary filers of citizen petitions.²³² The former FDA Chief Counsel Sheldon Bradshaw stated that petitions “appear designed not to raise timely concerns with respect to the legality or scientific soundness of approving a drug application, but rather to delay approval.”²³³ Former FDA Director Gary Buehler explained that it “is very rare that petitions present new issues that [the FDA’s Center for Drug Evaluation and Research] has not fully considered [V]ery few of these petitions on generic drug matters have presented data or analysis that significantly altered FDA’s policies.”²³⁴ Brand companies have significant incentives to file to delay generic competition. Their filing may delay ANDA approval even if their petition is not granted. In addition, it is inexpensive to file, and there are no consequences for filing frivolous petitions. Brand firms use these petitions as part of a comprehensive strategy, which also includes reverse-payment patent settlements and “product hopping,” to delay generics’ entry into the market.²³⁵

²³¹ Michael A. Carrier & Daryl Wander, *Citizen Petitions: An Empirical Study*, 34 CARDOZO L. REV. 249, 260 (2012).

²³² *Id.* at 252 (“The study finds that brand drug companies file 68% of petitions, far more than generic firms or other parties such as universities, doctors, or hospitals. Of the petitions by brand firms, more than 75% target generic entrants.”).

²³³ Marc Kaufman, *Petitions to FDA Sometimes Delay Generic Drugs*, WASH. POST (July 3, 2006), <http://www.washingtonpost.com/wp-dyn/content/article/2006/07/02/AR2006070200840.html> (quoting Sheldon Bradshaw, Chief Counsel, FDA) (internal quotation marks omitted).

²³⁴ *The Generic Drug Maze: Speeding Access to Affordable Life-Saving Drugs: Hearing Before the S. Spec. Comm. on Aging*, 109th Cong. 15 (2006) (statement of Gary Buehler, Director, Office of Generic Drugs, Center for Drug Evaluation and Research, FDA), available at <http://www.gpo.gov/fdsys/pkg/CHRG-109shrg30710/pdf/CHRG-109shrg30710.pdf>.

²³⁵ Carrier & Wander, *supra* note 231, at 278–79. “Reverse-payment settlements” refer to

Despite the benefits of further involving third parties in pharmacovigilance, granting parties with industry-adverse motivations access to HIE data presents hazards as well. Just as there is a concern that product sponsors will publish biased research, industry-adverse research sponsors could be biased. Researchers with an incentive to find evidence that a drug is harmful may find such evidence regardless of whether a causal relationship exists, and rival manufacturers might use this data to support vexatious actions, just like brand firms with citizen petitions. Policymakers should consider third parties' potential biases to help prevent unjust injury to pharmaceutical manufacturers.

E. NEW USES AND NEW USE PATENTS

Existing stakeholders currently have another incentive to data mine HIEs: they can use HIEs to discover new drug indications. Researchers can use observational data to uncover unexpected benefits as well as adverse events. Pharmaceutical manufacturers have a strong financial motive to discover new indications because they enlarge a drug's market. Manufacturers can apply to the FDA to add indications to a drug's label through a supplemental new drug application. Currently this occurs infrequently since approval generally requires costly new clinical trials.²³⁶ If manufacturers conduct new clinical trials, they also run the risk that they

agreements in which patentees (brand companies) pay challengers (generics companies) to settle a patent suit, unlike typical agreements in which the opposite occurs. *Id.* at 257 n.25. This is done so that generics companies will drop challenges to brand company patents that might be invalidated. *Id.* at 259. "Product hopping" occurs when brand companies make modest changes to on-patent drugs with patents that are about to expire in order to delay generic competition. For example, this might involve switching from a capsule to a tablet, or to an extended-release drug. Product hopping can help brand companies to avoid the effect of state drug product substitution ("DPS") laws that allow or require pharmacists to substitute generic versions of brand-name prescriptions. *Id.* at 252–53. The Supreme Court has recently held that reverse patent settlements may violate antitrust laws, and that the antitrust question should be answered by considering traditional antitrust factors. *FTC v. Actavis, Inc.*, 133 S. Ct. 2223, 2227 (2013).

²³⁶ Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358

will produce evidence that a drug is not effective for a new indication or even that it has safety problems, which is what happened to Vioxx. Observational data may reduce these risks because, if observational research demonstrates a positive correlation between an approved drug and a new indication, it is far more likely that clinical trials will show the same positive correlation. Even though it is expensive to conduct new trials, companies have good reason to seek FDA approval as it permits them to market the new indication to physicians. If the FDA approves a new use, the drug will receive a three-year period of market exclusivity for that indication.²³⁷ This means that even if generic drugs are already on the market, only the brand name drug could be marketed for the new indication. While generics companies can also submit applications for new uses, they are less likely to possess the resources to conduct costly trials.

Whatever a drug's approved uses, once a drug is on the market, physicians can prescribe it for any indication they choose. Although most prescriptions are for FDA-approved indications, referred to as *on-label* use, *off-label* use is common and legal; it accounts for around one-fifth of all prescriptions.²³⁸ Thus, evidence that a drug may be effective for an unapproved indication can motivate physicians to prescribe for that use even without FDA approval for that use. This explains why pharmaceutical manufacturers engage in corporate misbehavior, by encouraging off-label use, despite the FDA's strict restrictions on how pharmaceutical manufacturers can market their drugs for unapproved indications. As just one example of this misbehavior, in 2009, Pfizer paid a \$2.3 billion fine for illegally marketing several of its drugs.²³⁹ At the time, this was

NEW ENG. J. MED. 1427, 1427–29 (2008).

²³⁷ Abbott, *supra* note 169, at 71.

²³⁸ Stafford, *supra* note 236, at 1427–28.

²³⁹ Gardiner Harris, *Pfizer Pays \$2.3 Billion to Settle Marketing Case*, N.Y. TIMES (Sept. 2, 2009), <http://www.nytimes.com/2009/09/03/business/03health.html>.

the largest health care fraud settlement in history and the largest criminal fine of any kind.²⁴⁰ A former sales representative initiated this case and received more than \$50 million for his role in the litigation.²⁴¹ He was not the only one; from just the federal settlement, six whistle-blowers collected more than \$100 million.²⁴² However, from a corporate point of view, the fine could have been considered a routine cost of doing business since the entire fine amounted to less than three weeks of Pfizer's sales.²⁴³

HIE data could also be the basis for patenting new uses²⁴⁴ because the discovery that a known composition has a new use, based on the composition's unknown properties, may be patentable subject matter.²⁴⁵ Thus, pharmaceutical manufacturers have an incentive to get new use patents and use them to extend their period of market exclusivity. In general, while a drug is on patent, only the patent holder can make, use, offer to sell, sell, or import the drug for twenty years (the patent's term).²⁴⁶ While a process patent on a new use cannot prevent generics companies from selling the drug, it can prevent others from marketing the drug for the new

²⁴⁰ See *BP to Pay Record Fine in Gulf Oil Spill; 2 to Face Manslaughter Charges*, CBS News (Nov. 15, 2012, 9:45 AM), http://www.cbsnews.com/8301-201_162-57550185/bp-to-pay-record-fine-in-gulf-oil-spill-2-to-face-manslaughter-charges/.

²⁴¹ Harris, *supra* note 239.

²⁴² *Id.*

²⁴³ *Id.*

²⁴⁴ See, e.g., *In re Spada*, 911 F.2d 705, 708 & n.4 (Fed. Cir. 1990) (noting that "a new use of a known composition . . . may be patentable as a process").

²⁴⁵ See, e.g., *In re Hack*, 245 F.2d 246, 248 (C.C.P.A. 1957); see also U.S. PATENT & TRADEMARK OFFICE, MANUAL OF PATENT EXAMINING PROCEDURE § 2112 (8th ed. 2001). Whether a new use of an existing compound is patentable is a complex subject. Claiming a new use that is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254 (C.C.P.A. 1977). A new use may be inherently anticipated when the claim recites an existing composition and the use directed to a result or property of that composition. See, e.g., U.S. PATENT & TRADEMARK OFFICE, *supra*, § 2131.01.

²⁴⁶ 35 U.S.C. § 271(a) (2006).

indication.²⁴⁷ This essentially gives the patent holder a marketing monopoly for that indication, above and beyond anything granted by the FDA on the original product patent. In theory, such patents should have limited utility because physicians should know that they could still substitute a generic. But, in practice, perhaps due to effective physician detailing, physicians may prescribe brand name medicines for new uses.

Parties other than the product sponsor may obtain new use patents. If a product sponsor holds a primary patent on a drug and another party holds a patent for a new use, the product sponsor may prevent the third party from selling the drug during the primary patent's term. However, after the primary patent expires, the new use patent holder may enforce its patent against any party including the product sponsor (in relation to marketing for the new use). In practice, most third parties patent new indications and hope that a product sponsor will either buy out their patent or license it. Product sponsors are not the only parties interested in these patents; generic companies may also be interested either to try and establish their own marketing monopoly or just for defensive use.

F. *IN SEARCH OF NEW INCENTIVES—LOOKING TO QUI TAM LITIGATION*

Although third parties already have financial reasons to participate in the pharmacovigilance process, their incentives pale by comparison to the pharmaceutical industry's incentives. To have a truly balanced regulatory system, both sides of the equation should have equally committed representation. There are numerous mechanisms policymakers could introduce to address this problem, and the ideal solution may be a mix of proposals offering a variety of incentives. For example, a stronger and more direct regulatory approach might create

²⁴⁷ WENDY H. SCHACHT & JOHN R. THOMAS, CONG. RESEARCH SERV., RS21129, PHARMACEUTICAL PATENT TERM EXTENSIONS: A BRIEF EXPLANATION 3 (2002), *available at* <http://www.law.umaryland.edu/marshall/crsreports/crsdocuments/RS21129.pdf>.

new requirements for product sponsors to keep their drugs on the market. A new approach might require sponsors to directly conduct or fund meaningful post-approval clinical trials and observational research. Or legislation could place a new tax on drug manufacturers that would provide funding to the NIH to either conduct post-market surveillance directly or to award grants to academic health centers through a competitive program. Alternatively, the government could simply earmark a substantially increased amount of public funds to support pharmacovigilance research based on HIEs.

Yet these models would not directly address the problem of balance in the advocacy process. The public deserves an advocate as equally committed to challenging the safety and efficacy of approved drugs as product sponsors are to maintaining these drugs on the market.²⁴⁸ There is reason to think that a balanced adversarial system is desirable. Among other benefits, it would provide an added level of transparency and reinforce the norm of organized skepticism,²⁴⁹ which requires exposure of evidence of scientific claims to critical scrutiny.²⁵⁰

Assuming a more balanced adversarial model is desirable, private attorney general

²⁴⁸ As an analogy, in the securities field, the Securities Exchange Commission (“SEC”) has noted “private litigation enables a level of compliance that would be impossible to achieve if enforcement were limited to the government.” William B. Rubenstein, *On What a “Private Attorney General” Is—And Why It Matters*, 57 VAND. L. REV. 2129, 2151 (2004) (internal quotations marks omitted).

²⁴⁹ BIDDLE, *supra* note 122, at 2. Robert K. Merton introduced the term “organized skepticism” in 1942; he claimed it was one of four imperatives that scientific communities should exhibit if they are to produce epistemically reliable research. Robert K. Merton, *A Note on Science and Democracy*, 1 J. LEGAL & POL. SOC. 115, 126 (1942). Earlier proposals have attempted to institutionalize similar adversarial proceedings, for example, a 1967 proposal by Arthur Kantrowitz sought to establish a “science court” that would arbitrate controversial scientific or technological issues with important policy implications. Arthur Kantrowitz, *Proposal for an Institution for Scientific Judgment*, 156 SCIENCE 763 (1967).

²⁵⁰ The case of Vioxx has been identified as one of the paradigmatic failures of organized skepticism. BIDDLE, *supra* note 122, at 13.

mechanisms could bring this adversarial model to bear.²⁵¹ There are many ways to accomplish this. For example, a non-litigation-based strategy might focus on the use of citizen petitions for regulatory review, which might require companies to go through a hearing process and expert review committees following approval.²⁵² However, standing alone, this would fail to adequately incentivize private parties to file petitions and, more importantly, to invest in the research that is necessary to challenge existing evidence. A litigation-based strategy might rely on citizen suits, which are lawsuits by private citizens to enforce a statute.²⁵³ These are particularly common in the field of environmental law, where they were enacted in recognition of the fact that environmental regulatory agencies were constrained by scarce resources, limited information, and political pressures.²⁵⁴ Yet, like citizen petitions, citizen suits have an incentive problem. Namely, they do not provide for awards to be paid to lawsuit initiators.²⁵⁵ While plaintiffs' attorneys can recover fees and costs, and litigation may result in penalties payable to the

²⁵¹ The phrase "private attorney general" broadly refers to any person who mixes public and private features in the adjudicative area. Judge Jerome Frank introduced the phrase in *Associated Industries v. Ickes*, a 1943 Second Circuit case concerning the New Deal regulatory scheme. Jeremy A. Rabkin, *The Secret Life of the Private Attorney General*, 61 L. & CONTEMP. PROBS. 179, 182 (1998). Rabkin's piece reviewed the actions of private attorneys general. *See generally id.*

²⁵² In the field of environmental enforcement, citizen groups play an important role in monitoring and regulation. Rubenstein, *supra* note 248, at 2146–47.

²⁵³ *See, e.g.*, 33 U.S.C. § 1365 (2006) (codifying the Clean Water Act). Under the Clean Water Act ("CWA") citizens may sue other citizens, corporations, or the government for engaging in prohibited conduct. Citizens may also sue a government agency for failing to perform a non-discretionary duty.

²⁵⁴ Jonathan H. Adler, *Stand or Deliver: Citizen Suits, Standing, and Environmental Protection*, 12 DUKE ENVTL. L. & POL'Y F. 39, 43 (2001). Beginning in 1970, Congress enacted environmental citizen-suit provisions to enable third parties to supplement government enforcement efforts. *Id.* Citizen suits were also thought to protect against agency capture. *See, e.g.*, Barry Boyer & Errol Meidinger, *Privatizing Regulatory Enforcement: A Preliminary Assessment of Citizen Suits Under Federal Environmental Laws*, 34 BUFF. L. REV. 833, 843 (1985) ("The modern citizen suit provisions were first enacted at a time when 'capture' theories dominated scholarly and popular thought about regulation.").

²⁵⁵ Adler, *supra* note 254, at 45.

government, there are no direct financial rewards for plaintiffs.²⁵⁶ This suggests that citizen suits will not adequately incentivize third parties in the HIE context, where data analysis is costly, and where even in purely academic settings medical research is funding driven.

Some new form of administrative bounty proceeding (hereafter simply called a “bounty proceeding”) may be needed to incentivize third parties to submit information to the FDA. An effective bounty proceeding could have a variety of structures. It makes sense to model the proposed bounty proceeding after a proven system: qui tam litigation. This Article provides the first proposal to use qui-tam-type litigation to support pharmacovigilance; however, qui tam litigation is already a core method used to combat medical and pharmaceutical fraud and abuse under the False Claims Act (“FCA”).²⁵⁷

While a variety of civil and criminal statutes are used to combat fraud and abuse, the FCA²⁵⁸ is one of the most important.²⁵⁹ “Fraud and abuse” describes activities ranging from negligent overbilling, to self-referral arrangements, to outright fraudulent schemes by criminal enterprises billing for non-existent services; fraud and abuse is a serious problem for the government.²⁶⁰ Although it is difficult to accurately evaluate, improper payments under

²⁵⁶ Michael S. Greve, *The Private Enforcement of Environmental Law*, 65 TUL. L. REV. 339, 341 (1990) (stating that “environmental citizen-plaintiffs are supposed to be altruists”).

²⁵⁷ Qui tam actions and the False Claims Act have a long history. FCA is also known as the “Lincoln Law” because it was passed during Abraham Lincoln’s administration in response to widespread fraud during the Civil War. For a brief history, see J. Randy Beck, *The False Claims Act and the English Eradication of Qui Tam Legislation*, 78 N.C. L. REV. 539, 555–65 (2000). The Copyright Act also once had a qui tam provision for false entries of copyright. See John Tehranian, *Curbing Copyblight*, 14 VAND. J. ENT. & TECH. L. 993, 1027–28 (2012) (describing copyright’s long-forgotten private attorney general provision that endured from 1802 through 1909).

²⁵⁸ 31 U.S.C. §§ 3729–3733 (2006 & Supp. V 2011).

²⁵⁹ FURROW ET AL., *supra* note 11, at 1024.

²⁶⁰ *Id.* at 1023–24.

Medicare and Medicaid are estimated at a staggering \$70 *billion* annually.²⁶¹ Because fraud is such a significant financial drain, the government vigorously pursues claims against potential violators.²⁶²

Under the FCA, the federal government may recover substantial judgments from individuals who knowingly submit false claims; the government can recover 3 times its damages plus \$5500 to \$11,000 in civil penalties per claim.²⁶³ In 2012, the federal government recovered approximately \$3 billion from FCA cases.²⁶⁴ Although these recoveries may have had a valuable sentinel effect²⁶⁵ on other providers, the amount recovered represents only a fraction of the amount the Centers for Medicare and Medicaid Services (“CMS”) pays out in false claims.²⁶⁶

Congress has recognized that the government lacks the resources or ability to adequately combat false claims by itself, so it permits private qui tam actions that enable private individuals to enforce the FCA.²⁶⁷ The DOJ has come to rely upon private parties, known under the statute

²⁶¹ U.S. GOV’T ACCOUNTABILITY OFFICE, GAO-11-409T, MEDICARE AND MEDICAID FRAUD, WASTE, AND ABUSE: EFFECTIVE IMPLEMENTATION OF RECENT LAWS AND AGENCY ACTIONS COULD HELP REDUCE IMPROPER PAYMENTS (2011), *available at* <http://www.gao.gov/new.items/d11409t.pdf>. Moreover, these are the more easily detected cases.

²⁶² *Enforcement: DOJ Says Health Care False Claims Act Cases Yielded \$3 Billion in Recoveries in FY 2012*, HEALTH L. REP., Dec. 6, 2012, *available at* Bloomberg BNA: Health Law Res. Ctr., 21 HLR 1687.

²⁶³ 31 U.S.C. § 3729(a)(1)(G).

²⁶⁴ *See Enforcement: DOJ Says Health Care False Claims Act Cases Yielded \$3 Billion in Recoveries in FY 2012*, *supra* note 262.

²⁶⁵ The sentinel effect refers to the tendency for performance to improve when behavior is being evaluated. In the health care fraud and abuse context, a few high-profile judgments against health care providers may limit fraud and abuse more widely as the community perceives an increased risk of enforcement. D. McCarty Thornton, “*Sentinel Effect*” Shows Fraud Control Effort Works, 32 J. HEALTH L. 493 (1999).

²⁶⁶ *See supra* note 261 and accompanying text.

²⁶⁷ 31 U.S.C. § 3730(b) (2006). As an aside, the Department of Justice (“DOJ”) enforcement under the FCA for Medicare and Medicaid Fraud is another setting where data mining has proven an effective enforcement mechanism. Statistical analysis of claims can turn up suspicious billing patterns, such as where providers are billing over 24 hours of services in a single day. *See*

as “relators,” to identify cases for prosecution.²⁶⁸ In return, relators receive a percentage of the government’s final recovery against the defendant.²⁶⁹ This process does not restrict the government’s ability to bring suit on its own behalf.²⁷⁰ In fact, if the government is already party to an action, private parties can no longer bring a qui tam action.²⁷¹

Qui tam actions are now the principal way that the government uncovers fraud. In 2011, 92% of all government false claims actions were initiated in this manner.²⁷² Additionally, qui tam actions have proliferated; after a decade of filings averaging from 300 to 400 new cases annually, 2011 “marked the first time that new filings exceeded 600 in a single year.”²⁷³ The health care sector is the largest source of qui tam litigation. In 2011, health care accounted for 81% of qui tam recoveries, followed by defense at 6% of recoveries, and all other areas at 13% of recoveries.²⁷⁴ Within health care, the pharmaceutical industry is heavily represented.²⁷⁵ In 2011, FCA recoveries involving the pharmaceutical industry were \$2.2 billion.²⁷⁶

G. MODELING A BOUNTY PROCEEDING AFTER AN FCA QUI TAM ACTION

Michael Volkov, *Health Care Fraud Enforcement: Current Trends*, CORRUPTION, CRIME & COMPLIANCE (July 3, 2012), <http://corruptioncrimecompliance.com/2012/07/health-care-fraud-enforcement-current-trends/>.

²⁶⁸ Aaron S. Kesselheim, *Whistle-Blowers’ Experiences in Fraud Litigation Against Pharmaceutical Companies*, 362 NEW ENG. J. MED. 1832, 1832–34 (2010).

²⁶⁹ 31 U.S.C. § 3730(d).

²⁷⁰ *Id.* § 3730(c)(3).

²⁷¹ *Id.* § 3730(e)(3) (“In no event may a person bring an action under subsection (b) which is based upon allegations or transactions which are the subject of a civil suit or an administrative civil money penalty proceeding in which the Government is already a party.”).

²⁷² Elizabeth Wang, *Qui Tam Trends in 2011, Predictions for 2012*, LAW360 (Feb. 8, 2012, 1:08 PM), <http://www.law360.com/articles/307145/qui-tam-trends-in-2011-predictions-for-2012>.

²⁷³ *Id.*

²⁷⁴ *Id.*

²⁷⁵ See *Allegations of Waste, Fraud, and Abuse in Pharmaceutical Pricing: Financial Impacts on Federal Health Programs and the Federal Taxpayer: Hearing Before the H. Comm. on Oversight and Gov’t Reform*, 110th Cong. (2007), available at <https://bulk.resource.org/gpo.gov/hearings/110h/35340.pdf>.

²⁷⁶ Wang, *supra* note 272.

The bounty proceeding proposed in this Article would provide petitioners an award if they presented the FDA with original data documenting a drug safety or efficacy concern that resulted in amended product labeling or the withdrawal from market of an approved drug or device. Because a bounty proceeding would not be limited to a suit for damages on behalf of the government, the proposed bounty proceeding would not technically be a *qui tam* action.²⁷⁷ However, to the extent that it is practicable, an FCA *qui tam* action can serve as a model for structuring a bounty proceeding. After all, the government, industry, and third parties have extensive experience with the FCA model. Before creating a bounty proceeding policymakers must address some core procedural decisions to ensure that the system will function effectively.

1. *STANDING AND SETTLEMENT*

Who should have standing to bring a bounty proceeding? In an FCA *qui tam* action, a relator is generally a whistleblower with insider knowledge about his or her employer's illegal activities.²⁷⁸ In contrast, a bounty proceeding would be more concerned with incentivizing

²⁷⁷ *Qui tam* liability may be limited to suits for damages on behalf of the government. Compare *Vt. Agency of Natural Res. v. United States ex rel. Stevens*, 529 U.S. 765 (2000), with *Lujan v. Defenders of Wildlife*, 504 U.S. 555 (1992). This comparison suggests that a *qui tam* action for a pure penalty would violate Article II of the Constitution by delegating law enforcement to a private party. One district court has so held with respect to the False Patent Marking *qui tam* provision. *Stauffer v. Brooks Bros., Inc.*, 619 F.3d 1321, 1324–27 (Fed. Cir. 2010).

²⁷⁸ 31 U.S.C. § 3730(e)(4)(B) (2006 & Supp. IV). However, the scope of who can qualify as a relator was recently expanded under the Fraud Enforcement and Recovery Act of 2009 (“FERA”) and the ACA. Prior to the ACA, *qui tam* actions were barred if the issue in the suit had been publically disclosed in a “congressional, administrative, or [GAO] report, hearing, audit, or investigation.” 31 U.S.C. § 3730(e)(4)(A) (2006) (amended 2010). This prohibition included information disclosed in federal hearings, audits, or investigations, as well as state and local administrative proceedings. Now, “public disclosure” is limited to reports of *federal* criminal, civil, and administrative proceedings, in which the “government or its agent is a party.” Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 1303(j)(2), 124 Stat. 119 (2010) (codified at 31 U.S.C. § 3730(e)(4)(A) (2006 & Supp. IV)). This allows relators to bring suit solely on the basis of information already in the public domain. *Id.* The ACA also removed the requirement that a relator must be an “original source” with “direct and independent

independent research. Post-market data hostile to the interests of product sponsors is not necessarily due to corporate malfeasance, and if a company already has such data, it is required to present it to the FDA.²⁷⁹ In fact, failure to do so would result in liability under the FCA.²⁸⁰ Rather than involving insiders, a bounty proceeding would more likely involve outsiders with independently generated research. This suggests that a bounty proceeding should not be overly concerned with limiting the scope of potential petitioners.

However, to prevent abuses, there should be certain limitations on who may qualify as a petitioner. For example, if an academic research group publishes a study in a peer-reviewed medical journal that questions a drug's safety, there is limited societal utility in rewarding a different third party simply for submitting that study to the FDA. The cause of action is intended to create new knowledge, not for a third party to merely utilize knowledge in the public domain. So, to be a proper petitioner, a party should have a significant role in generating the data or analysis—for instance, through that party's own data mining or clinical research. Although, ideally, aggregated HIE data would be in the public domain for pharmacovigilance purposes, the statistical analyses performed by petitioners would need to be original. When multiple parties perform the same analyses on the same data, future redundant submissions should be barred once a party submits the data in a bounty proceeding. However, it is possible that multiple parties might independently submit research that contributes jointly to an FDA determination. In that case, the FDA could apportion an award between petitioners at its discretion. This is similar to

knowledge” of an alleged violation. *Id.* A relator may now qualify if he or she voluntarily provides information to the government prior to its public disclosure or if he or she “has knowledge that is independent of and materially adds to the publicly disclosed allegations or transactions” at issue. 31 U.S.C. § 3730(e)(4)(B) (2006 & Supp. IV).

²⁷⁹ See THAUL, *supra* note 87, at 12.

²⁸⁰ *Id.*

the FCA's system, in which the U.S. attorney general has the authority to apportion the award between relators.²⁸¹

Parties may also abuse the system if they submit insignificant data in an attempt to obtain a windfall or to harass a product sponsor. A third party may strategize that if it submits immaterial data on a drug's risk-benefit profile, and the FDA withdraws the drug on some other basis, the petitioner may share in a judgment. To deal with this possibility, under the proposed bounty proceeding, the FDA would have to determine that a petitioner's submission materially added to the FDA's evaluation before the petitioner may recover an award. Specifically, the FDA should find that "but for" the administrative bounty submission, the revised FDA determination would not have occurred. The possibility that parties may file vexatious actions will concern product sponsors. One might expect these actions if the petitioner is a rival manufacturer or a personal injury firm. To prevent possible abuse both the FDA and product sponsors should have access to petitioner data, analytical methods, algorithms, etc. Also, under the proposed proceeding, the FDA could act as a gatekeeper. In other words, only submissions that the FDA determines are significant and meritorious would be passed along to product sponsors and used as the basis for reviewing a product's approval. An influx of baseless submissions would stress the FDA's limited resources. To minimize frivolous submissions, the FDA could award attorneys' fees or certain costs to the product sponsor if a submission was found to lack merit. The FDA could also collect user fees from petitioners to supplement its capacity to review these applications. If product sponsors are subject to an adverse determination, they could be

²⁸¹ 12 U.S.C. § 4205(d)(2)(A) (2012) ("When more than 1 declarant has provided information leading to a recovery under this subsection, the Attorney General shall first calculate the size of the total award . . . and then distribute that amount according to the contribution made by each declarant.").

responsible for these fees.

Because modern biomedical research is often a large-scale undertaking with many participants, this further complicates the question of who should qualify as a proper petitioner. At a single university, several researchers may be responsible for a study's output. Moreover, it is also common for investigators at multiple institutions to collaborate and for projects to be extramurally funded, for example by government, industry, or non-profits. Policymakers designing the bounty proceeding incentive structure should not seek to limit collaboration or external sources of funding since both mechanisms are vital to the research process. The best option for dealing with these complexities may be to model award distributions after existing rules for distributing intellectual property rights ("IPR"s). Today, most relationships between research institutions and their employees, between collaborating organizations, and between funding agencies and grant recipients are governed by contract. In particular, universities have become sophisticated IPR bargainers ever since the Bayh-Dole Act permitted universities, small businesses, and non-profits to own the IPRs developed from federal government-funded research.²⁸² The market for commercializing university research results is thriving.

Universities could treat bounty proceeding awards similar to IPRs. Currently, universities often require their employees to assign them the right to any IPRs the employee develops, perhaps with the researchers retaining some financial interest.²⁸³ In any case, participants would be free to contract among themselves *ex ante*. Where such ownership questions have not been addressed through contract, default rules already exist that govern IPR ownership. Likewise, a

²⁸² 35 U.S.C. § 200–212 (2006 & Supp. V 2011); 37 C.F.R. § 401(2012).

²⁸³ Robert Kneller, *Intellectual Property Rights and University—Industry Technology Transfer in Japan*, 26 SCI. & PUB. POL'Y 113, 114 (1999) ("[N]early all US universities require their employees to assign to them rights in employment-related inventions . . .").

contract could govern bounty award distribution when research is based on work conducted by researchers at multiple institutions. Where no contract exists, the FDA should have discretion to apportion the award between parties, as in the case of multiple independent submissions. Finally, where an external body funds research, ownership of the resulting IPR can also be governed by contract, with a few special exceptions. As with other IPR forms, such as patents, when government grants fund university research, ownership should default to the university rather than to the government. Product sponsors would presumably want to contract to keep researchers from filing administrative bounty claims, but it would violate public policy to allow contracts to prevent adverse data from coming to light. The solution is to allow product sponsors to contract to prevent funding recipients from filing a bounty proceeding so long as the pharmaceutical company submits the data to the FDA. This would essentially be a first right to file; if the product sponsor fails to do so within a certain time frame, the right to file a bounty proceeding would revert to the funding recipient.

An additional consideration is that settlements between petitioners and product sponsors could undermine the bounty proceeding process. It would defeat the purpose of the proceeding if product sponsors could pay off petitioners to withdraw their submissions. This has been a problem with citizen suits under the Clean Water Act (“CWA”), and Congress subsequently amended the citizen suit provisions to give the Environmental Protection Agency (“EPA”) and the Attorney General a 45-day notice of consent judgment terms before they take effect in order to permit a government objection.²⁸⁴ However, “such review is fairly cursory in practice.”²⁸⁵ The best solution may be to prevent settlements between adverse parties in a bounty proceeding. Less

²⁸⁴ 33 U.S.C. § 1365(c)(3) (2006).

²⁸⁵ Adler, *supra* note 254, at 50.

ambitiously, any settlement agreement could require FDA approval.²⁸⁶

2. *VENUE*

After determining the criteria used to qualify petitioners, a second issue arises: What is the proper venue for a bounty proceeding? In FCA qui tam actions, a relator may file in federal district court.²⁸⁷ However, the federal courts are ill equipped to make safety and efficacy determinations. The FDA is the best potential arbitrator because of its agency expertise, its existing knowledge about the drug in question, and its mission as a protector of public health. For this reason, a bounty proceeding should take place in an FDA administrative hearing, which would create an adversarial process where one party seeks to maintain drug approval (or labeling) while the other seeks to have the drug withdrawn (or labeling amended).²⁸⁸ The administrative hearing this proposal envisions would be a sophisticated litigation-type process. The bounty proceeding would be a new type of procedure for the FDA to the extent that the agency does not currently render large monetary judgments to the benefit of private parties.

²⁸⁶ Alternately, settlements might simply be subject to standard Federal Trade Commission (“FTC”) review under traditional antitrust factors. *See* Cal. Dental Ass’n v. FTC, 526 U.S. 756, 775 n.12 (1999).

²⁸⁷ 31 U.S.C. § 3732(a) (2006).

²⁸⁸ In most states, if prescription drug labeling warns of a potential adverse reaction, the “learned intermediary doctrine” preempts a failure to warn product liability suit. *See* Sterling Drug, Inc. v. Cornish, 370 F.2d 82, 85 (8th Cir. 1966). This doctrine is based on the concept that a pharmaceutical manufacturer discharges its duty to warn users of the risks associated with its products by warning the prescribing physician. *See id.* West Virginia is the only state that has rejected the doctrine in its entirety. *Centocor, Inc. v. Hamilton*, 372 S.W.3d 140, 161 (Tex. 2012). As a result of this doctrine, pharmaceutical manufacturers may be incentivized to list as many adverse reactions as possible in the “warnings and precautions” section of labeling. This suggests manufacturers may not be opposed to the simple addition of adverse reactions in labels. However, the FDA has other means of influencing prescribing habits besides requiring the addition of adverse reactions or completely withdrawing a drug from market. These include “black box” warnings (bordered in black to signify their importance) and restrictions on distribution and use. THAUL, *supra* note 87, at 11. Researchers debate the effectiveness of adverse-reaction warnings in labeling, even in black box form. *See id.*

However, the FDA has the capability to adjudicate bounty proceedings with some modifications to existing administrative procedures.²⁸⁹ For example, bounty procedures could be modeled after the procedures for reviewing citizen petitions.²⁹⁰ The Commissioner (or an official to whom the Commissioner has delegated authority such as a center director) evaluates these petitions in a proceeding. The Commissioner may hold conferences, meetings, discussions, and maintain correspondence as part of the review process.²⁹¹ The Commissioner may also provide a formal evidentiary public hearing or a hearing before a Public Board of Inquiry.²⁹² In the case of a formal evidentiary public hearing, a responsible FDA center may conduct investigative functions and participate in a pleading or oral argument before the Commissioner, with attorney assistance available from the Office of the Chief Counsel.²⁹³

Regulatory hearings, over which a Commissioner appointed administrative law judge presides, could also provide a model for the bounty proceedings.²⁹⁴ Hearings are open to the public, except when the Commissioner determines that they should be closed to prevent invasion

²⁸⁹ For an overview of general FDA administrative proceedings, see 21 C.F.R. § 1.1 (2013).

²⁹⁰ For an overview of general administrative procedures for a citizen petition, see 21 C.F.R. § 10.30.

²⁹¹ *Id.* § 10.30(h).

²⁹² *See id.* § 13.1.

²⁹³ *See Office of the Chief Counsel, FDA*, <http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeoftheChiefCounsel/default.htm> (last updated Feb. 24, 2010) (“The Office of the Chief Counsel (OCC), which is the Food and Drug Division of the HHS Office of the General Counsel, is composed of litigators, counselors, and support staff. Litigators handle both civil and criminal enforcement cases, and defend challenges to provisions of the Federal Food, Drug, and Cosmetic Act (FDCA), the implementing regulations, and FDA policies, initiatives, and decisions. The litigators work closely with agency compliance personnel to ensure an adequate evidentiary foundation for enforcement matters, prepare referrals to the Department of Justice, draft memoranda setting out the agency’s interpretation of the law, develop case strategy, conduct negotiations, prepare and respond to discovery, and are key participants in hearings, trials, and appellate proceedings.”).

²⁹⁴ For an overview of regulatory hearing proceedings, see 21 C.F.R. § 16.1 and the surrounding sections.

of personal privacy or disclosure of confidential information.²⁹⁵ In a hearing, both FDA employees and the party requesting the hearing may present oral and written testimony, and all parties may confront and conduct reasonable cross-examination of any person making a statement.²⁹⁶ As the hearing is informal in nature, the rules of evidence do not apply; thus objections relating to the admissibility of information are not considered.²⁹⁷ However, any party may comment or rebut any presented data.²⁹⁸ The presiding officer is responsible for issuing “a finding on the credibility of witnesses (other than expert witnesses) whenever credibility is a material issue.”²⁹⁹ The presiding officer also issues “a recommended decision, with a statement of reasons, unless the Commissioner directs otherwise.”³⁰⁰

The FDA can assess civil monetary penalties for a range of activities including marketing practices, clinical trial data reporting, and spoliation of evidence.³⁰¹ Maximum penalties may apply to violations as established by statute or the Public Health Service Act.³⁰² Administrative civil money penalty actions have a separate body of procedural rules that governs issues including service of complaint, discovery, summary judgment, fees, burden of proof, evidence, and appeals.³⁰³

In sum, the FDA could adjudicate a bounty proceeding through a process that adopts

²⁹⁵ 21 C.F.R. § 16.60(a).

²⁹⁶ *Id.* § 16.60(b).

²⁹⁷ *Id.* § 16.60(c).

²⁹⁸ *Id.*

²⁹⁹ *Id.* § 16.60(f).

³⁰⁰ *Id.*

³⁰¹ The process for FDA Civil Money Penalties is governed by 21 C.F.R. §§ 17.1–17.54.

³⁰² For example, the maximum penalty in the case of a 21 USC § 333(f)(9)(B)(ii) (2006 & Supp. V 2011) violation is \$10,000,000. This relates to an intentional violation of tobacco product requirements where the violation continues after the FDA Secretary provides written notice of the violation.

³⁰³ *See* 21 C.F.R. § 17.7 (service of complaint); *id.* § 17.23 (discovery); *id.* § 17.33 (burden of proof).

elements of a citizen petition and regulatory hearing.³⁰⁴ Alternatively, the FDA could charter a new administrative body to render decisions. The FDA could largely implement this new system by itself as it has the general rulemaking authority to amend the licenses it issues and to allow private parties to petition for such action. However, congressional authorization would likely be required for an award to accompany a successful petition.

Although appeals to the federal courts should be permitted, appellate courts should be required to adhere to a highly deferential standard.³⁰⁵

H. *PAYING FOR A BOUNTY PROCEEDING*

For a bounty proceeding to mobilize third party participation like FCA qui tam litigation, the financial prizes must be adequate.³⁰⁶ As a comparison, FCA judgments are frequently

³⁰⁴ The FDA has additional resources that might contribute to a bounty proceeding. For example, the FDA Office of the Ombudsman is a neutral resource that helps to resolve disputes between private parties and FDA offices concerning application of FDA policy and procedures. It handles, for instance, disputes regarding District Office actions and import detentions, and coordination of appeals from decisions made by offices within the Office of the Commissioner under 21 C.F.R. § 10.75. For an overview of the FDA Ombudsman's process, see *The FDA Ombudsman*, FDA, <http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/ucm197508.htm> (last updated May 29, 2013).

³⁰⁵ Congress could articulate the requisite standard of review in legislation establishing a bounty proceeding. To the extent the agency is alleged to have gone beyond statutory bounds, either *Chevron* or *Skidmore* deference would apply under *Mead*. See *United States v. Mead Corp.*, 533 U.S. 218, 226–27 (2001). The relevant standard would depend on whether bounty proceedings are required to be implemented by formal adjudication, which would trigger *Chevron*, or informal adjudication, which would trigger *Skidmore*. See *id.*

³⁰⁶ FCA awards, which could provide a model for pharmacovigilance bounty proceeding awards, are based on a two-tiered system tied to a percentage of the funds the government receives. See 31 U.S.C. § 3730(d) (2006). Although private parties file qui tam actions, they have to give the government the opportunity to take over the case. *Id.* § 3730(b) (stating that an action may only be brought in the name of the government, and can only be dismissed if the court and the Attorney General give written consent). The complaint must be filed in camera, and a copy has to be submitted to the government, along with all material evidence. 31 U.S.C. § 3730(b)(2); see also BLACK'S LAW DICTIONARY 828 (9th ed. 2009) (defining “in camera” to mean “[i]n the judge’s private chambers” or “taken when court is not in session”). The complaint then remains

hundreds of millions of dollars.³⁰⁷ On the other hand, excessive awards risk over-incentivizing litigation with diminishing public benefit. The award should preferably be calibrated to the value of the public service the petitioner provides. While definitively calculating the ideal bounty size would require complex economic analysis beyond the scope of this Article, several broad options are worth discussing. There needs to be a general basis for calculating petitioner awards and, importantly, a source of financing.

Before addressing the closely related issue of who should bear the cost of bounties, and for now assuming in *arguendo* that product sponsors would be responsible, two theories of liability—strict liability and negligence—offer possibilities for calculating petitioner rewards. The simplest option may be a no-fault, strict liability regime in which the product sponsor would be liable for any adverse effects, regardless of whether there was any careless conduct or ill intent.³⁰⁸ A no-fault system makes it more likely petitioners will participate because they will not need to establish negligence in order to recover. Strict liability may be appropriate because drug

under seal for a minimum of 60 days, often longer, while the government decides whether to intervene. 31 U.S.C. § 3730(b); *see* FURROW ET AL., *supra* note 11, at 1050. “On average, the DOJ takes 13 months to review a case and decide whether to intervene as a plaintiff.” Wang, *supra* note 272. It is not served on the defendant until the court orders service. *Id.* If the DOJ decides to intervene and prosecute the case directly, and if it is successful in securing a judgment or settlement, a relator receives between 15% and 25% of the recovered amount. 31 U.S.C. § 3730(d). If the DOJ declines to intervene, a relator may recover between 25% and 30%. *Id.* However, if the DOJ declines to intervene, it is far less likely a relator will realize a recovery. In 2011, the DOJ only intervened in 22% of FCA qui tam filings, Elizabeth Wang, *Trends in Qui Tam False Claims Cases*, LAW360 (July 26, 2011, 1:56 PM), <http://www.law360.com/articles/258434/trends-in-qui-tam-false-claims-cases>, but 95% of recoveries were from cases in which the DOJ intervened, Wang, *supra* note 272. Regardless of intervention, successful relators are also entitled to legal fees. 31 U.S.C. § 3730(d). By contrast, an administrative bounty proceeding should not require an in camera filing requirement so as to better achieve its public safety goal.

³⁰⁷ Wang, *supra* note 272.

³⁰⁸ Strict liability makes a party legally responsible for damages they have caused regardless of culpability. In other words, even in the absence of fault or negligence. *See* BLACK’S LAW DICTIONARY 998 (9th ed. 2009).

companies can never ensure that their product is absolutely safe and effective before the FDA approves it.³⁰⁹ While a strict liability structure might create manufacturer liability for some non-negligent activity, a no-fault system would have positive externalities. The no-fault system provides an even stronger impetus for manufacturers to make best efforts to accurately evaluate new drug candidates, and reduces their drive to seek approval of unsafe drugs. For this reason, strict liability should lead to improved clinical research design and implementation.

Liability could also arise under a negligence-type theory tied to the time period that a product sponsor knew, or should have known, that its product had an unfavorable safety or efficacy profile. For example, if a company knew its product was not safe prior to approval, the manufacturer would be liable for any adverse effects that occurred during the drug's entire market lifecycle. However, if reason to know of the adverse effect only emerged in the drug's final year of use, then liability would only extend to events occurring within that year. This would incentivize manufacturers to diligently use HIE data once it become publically available, but this liability model would fail to incentivize drug sponsors to independently generate new data.

Because a bounty proceeding is more concerned with incentivizing outside research than with revealing insider information, it would not necessarily require petitioners to have a right to discover sponsor data during litigation. In fact, avoiding discovery would help to reduce sponsor compliance costs. However, if the FDA were to make an industry-adverse determination in light of a petitioner's submission, this could trigger a right to discovery. Discovery may be necessary to establish negligence. If discovery reveals that product sponsors knowingly failed to submit adverse data or if they did so recklessly or with gross negligence, they could be subject to

³⁰⁹ ABBOTT & DUKES, *supra* note 113, at 195.

enhanced liability.

Regardless of the theory on which liability is predicated, successful petitioners could either receive a flat fee bounty or a variable award. A flat fee bounty would provide a degree of certainty to all parties. However, one concern with a fixed award is that it would likely stimulate private actions that provide less social value. This has been a problem with citizen suits under the CWA.³¹⁰ In that setting, private actions create the most public benefit when they focus on pollution sources government does not already know about, but those are the most expensive and difficult to identify. Unfortunately, plaintiffs most often receive rewards for focusing on the cheapest and easiest pollution sources to identify, including those already identified in government filings.³¹¹

Alternatively, petitioners could receive a variable bounty. This could be based on drug revenue. Basing awards on drug revenue is advantageous because it stimulates intervention proportional to a drug's public health cost.³¹² A variable bounty will drive third parties to focus inquiries on the most widely used drugs because this may lead to a larger bounty. In addition, a determination that these products are unsafe or ineffective, and their withdrawal from the market, will create a correspondingly significant financial benefit to health insurers. To the extent that petitions uncover mild side effects in socially valuable drugs, this would result in revised

³¹⁰ See Greve, *supra* note 256, at 390–91.

³¹¹ *Id.*

³¹² Revenue is generally proportional to sales volume, and all things being equal, unsafe drugs with a larger sales volume will cause more patient injury. Alternatively, some drugs may generate relatively large revenue by virtue of being expensive, rather than due to sales volume. Some drugs are very expensive—at least 9 drugs cost over \$200,000 annually. Matthew Herper, *The World's Most Expensive Drugs*, FORBES.COM (Feb. 22, 2010, 6:00 AM), <http://www.forbes.com/2010/02/19/expensive-drugs-cost-business-healthcare-rare-diseases.html>. Alexion Pharmaceutical's Soliris has the distinction of being the world's most expensive drug, at a cost of \$409,500 per year. *Id.*

labeling and a relatively small petitioner recovery.

Determining the amount of a variable petitioner's reward would be a fact-intensive inquiry, requiring forensic evidence and expert testimony. It would be analogous to the process for determining damages in a personal injury action. In a bounty proceeding, the petitioner, the product sponsor, and potentially even the FDA would present an economic analysis. The petitioner would have an incentive to overestimate in order to maximize potential recovery, while the product sponsor's incentive would be to underestimate in order to minimize its own potential liability.

If a drug sponsor had to pay an award to a petitioner, the bounty proceeding system could allow the government to receive a share of that award. However, in most cases this may not be necessary. The government would already receive a benefit from taking ineffective and unsafe drugs off the market. The cost to industry may be less if the government does not require a share of an award, and that would be particularly desirable where there is no evidence the product sponsor had ill intentions. On the other hand, where negligence or negligence-plus is found, it may make sense to require the manufacturer to pay an award to the government as a punitive measure.³¹³ Alternatively, the increased award could go entirely to petitioners and would create an even stronger inducement for involvement.³¹⁴ Product sponsors should not be eligible for a

³¹³ Some states require that a portion of punitive damages in private attorney general actions must be distributed to public-benefit funds. For example, Iowa requires that 75% of punitive damages must be paid to a civil reparations trust fund. *See* IOWA CODE § 668A.1(2)(b) (2013); Rabkin, *supra* note 251, at 196–97. This is a minority practice, however, and not the practice in federal litigation. *See* Rabkin, *supra* note 251, at 196–97. For a comprehensive discussion of U.S. punitive damages regulation and theory, see Jessica J. Berch, *The Need for Enforcement of U.S. Punitive Damages Awards by the European Union*, 19 MINN. J. INT'L L. 55, 62–77 (2010) (canvassing punitive damages statutes and case law).

³¹⁴ The theory underlying punitive damages is that that willful or reckless tortfeasors should suffer a penalty beyond paying for actual damages. *See* BLACK'S LAW DICTIONARY 448 (9th ed.

petitioner's reward from the government in the event they sponsor research that the FDA uses to withdraw a drug from the market. The proposed bounty system already provides the industry with an incentive to conduct follow-up research and to limit its own liability to petitioners.

I. COST BEARERS

Under any liability standard, the proposed bounty system will require funding. Where will the money come from? One option is for the pharmaceutical industry to bear the cost of paying the bounties. Under this model, a petitioner could commence a bounty proceeding by submitting evidence that a drug is unsafe or ineffective, and if the FDA determines that a drug should be withdrawn from market, the product's sponsor would be responsible for paying a reward, assessed as a function of drug revenue or as a fixed fee, to the petitioner. There are a number of benefits to putting this cost on the industry. First, manufacturers are the cheapest cost avoiders of adverse drug effects because they have the best opportunity to seek out problems.³¹⁵ Having industry bear the cost would further encourage it to guard against product defects. The industry is also a natural cost bearer because it derives the most direct financial benefits from drug approval. However, the pharmaceutical industry has long claimed it needs special protections to encourage innovation, drug discovery, and commercialization because these activities have high costs.³¹⁶ It makes these arguments even though brand-name drugs have high

2009). Enhanced damages provide a deterrent effect regardless of who receives the penalty, but allowing plaintiffs to receive punitive damages encourages lawsuits beneficial to the public. *See* Clayton Antitrust Act, 15 U.S.C. § 15(a) (2012).

³¹⁵ In other words, placing the burden on the pharmaceutical industry would minimize the "sum of accident costs and of costs of avoiding accidents." Guido Calabresi & A. Douglas Melamed, *Property Rules, Liability Rules, and Inalienability: One View of the Cathedral*, 85 HARV. L. REV. 1089, 1094 (1972).

³¹⁶ Billy Tauzin, President & Chief Exec. Officer, PhRMA, Keynote Address Before the American Legislative Exchange Council Annual Dinner: Putting Patients First to Keep Health Care in America the Best in the World Putting Patients First to Keep Health Care in America the

profit margins,³¹⁷ and brand firms make annual profits of between 15% and 20% (far above other industry profit margins).³¹⁸ The industry consistently criticizes tort liability, and it advocates for tort reform, claiming that existing liability discourages and destroys innovation.³¹⁹ The industry raises similar arguments to protest government regulation of medicines.³²⁰

Health insurers are a second natural source of funding because they currently bear ineffective and unsafe medicines' costs. While the proposed bounty system may require some up-front financing from insurers, in the long run it may reduce costs. Instead of basing petitioner awards on a portion of drug revenue, they might be based on a percentage of insurers' projected savings.

Unsafe and ineffective medicines create substantial costs for insurers, but these costs are more difficult to measure than a drug's revenue.³²¹ For example, it is estimated that all adverse

Best in the World (Aug. 2, 2005), available at <http://phr-dev.wcgwork.com/news-media/speeches/putting-patients-first-keep-health-care-america-best-world-putting-patients-firs>.

³¹⁷ Connors, *supra* note 100, at 246.

³¹⁸ DANIEL CALLAHAN & ANGELA A. WASUNNA, *MEDICINE AND THE MARKET: EQUITY V. CHOICE* 165 (2006).

³¹⁹ Louis Lasagna, *The Chilling Effect of Product Liability on New Drug Development*, in *THE LIABILITY MAZE: THE IMPACT OF LIABILITY LAW ON SAFETY AND INNOVATION* 334, 334–43 (Peter W. Huber & Robert E. Litan eds., 1991).

³²⁰ ABBOTT & DUKES, *supra* note 113, at 209–10.

³²¹ Controversially, Professor Philippe Even, director of the Necker Institute, and Bernard Debré, a physician and member of the French parliament, claim that 50% of the approved medicines on the French market are therapeutically useless, “20% are badly tolerated, and 5% are potentially dangerous.” Germán Velásquez, *New Study Shows the Crisis of Ineffective and Unsafe Medicines*, S. CENTRE, http://www.southcentre.org/index.php?option=com_content&view=article&id=1862%3Asb68&catid=144%3Asouth-bulletin-individual-articles&Itemid=287&lang=en (last visited Aug. 24, 2013). They claim that potentially dangerous medicines cause nearly 100,000 serious adverse events each year requiring hospitalization, and 20,000 medication-related deaths. *Id.* They further claim that removing these drugs from market would save France up to €15 billion annually. *Id.*; see also Kim Willsher, *Half of Drugs Prescribed in France Useless or Dangerous, Say Two Specialists*, *GUARDIAN* (Sept. 14, 2012, 12:18 PM), <http://www.guardian.co.uk/world/2012/sep/14/french-doctors-drugs-useless-dangerous/>.

drug reactions (not only those which occur as a result of unsafe drugs) account for up to 6% of hospital admissions,³²² 28% of emergency department visits,³²³ and 5% of hospital deaths.³²⁴ If petitioner awards were based on a percentage of insurers' projected savings, there would have to be a factual inquiry and economic analysis on a case-by-case basis to determine the cost to insurers.

Although the insurance industry could be made to bear the entire program's costs, the insurance industry, like the pharmaceutical industry, complains vociferously about a high degree of regulation and industry-specific taxes.³²⁵ While the health care insurance industry as a whole may ultimately save money under such a system, it is likely to strongly oppose upfront costs without a guaranteed short-term return.

One health care insurer in particular may be well situated as a cost bearer: the federal government—the nation's largest direct financier, insurer, and health care provider.³²⁶ The federal government has deep pockets and the ability to make long-term investments. It makes sense for the government to finance this system, given that it would be the ultimate beneficiary. Unsafe and ineffective drugs are not merely private problems; they affect the economy as a whole, as a result of direct costs for medical expenditures and indirect costs for diminished productivity.³²⁷ Therefore, the government would benefit directly from avoiding the costs of ineffective and

³²² Munir Pirmohamed et al., *Adverse Drug Reactions*, 316 BRIT. MED. J. 1295, 1295 (1998).

³²³ Payal Patel & Peter J. Zed, *Drug-Related Visits to the Emergency Department: How Big Is the Problem?*, 22 PHARMACOTHERAPY 915, 915 (2002).

³²⁴ L. Juntti-Patinen & P.J. Neuvonen, *Drug-Related Deaths in a University Central Hospital*, 58 EUR. J. CLINICAL PHARMACOLOGY 479, 480 (2002).

³²⁵ TIMOTHY STOLTZFUS JOST, *THE REGULATION OF PRIVATE HEALTH INSURANCE* 8–30 (2009), available at http://www.nasi.org/usr_doc/The_Regulation_of_Private_Health_Insurance.pdf.

³²⁶ LUCY STRIBLEY ET AL., *THE FEDERAL GOVERNMENT'S KEY ROLE IN HEALTHCARE INNOVATION* 1 (2012), available at <http://www.boozallen.com/media/file/The-Federal-Governments-Key-Role-in-Healthcare-Innovation-wp.pdf>.

³²⁷ PAUL STARR, *THE SOCIAL TRANSFORMATION OF AMERICAN MEDICINE* 236 (1982).

unsafe drugs and indirectly from improved patient outcomes that would lead to higher productivity and increased tax revenue.³²⁸ Financial ramifications aside, government interests align with improved patient outcomes because the government directly represents the American public, unlike private insurance companies that represent shareholders and that are in business to earn profit. The government has an “interest in the health and well-being—both physical and economic—of its residents in general.”³²⁹ While government spending is never politically popular, the government comes out ahead if petitioner awards are merely a percentage of the money the government saves.

In sum, policymakers could combine the previously discussed standards of liability, methods to calculate the size of petitioner rewards, and proposals of who should pay to structure a bounty proceeding in the following manner. If a petitioner submission results in the FDA removing a product from the market or amending labeling, the federal government could pay the petitioner a reward based on the government’s estimated cost savings over a determined time period. If the proceeding establishes that the product’s sponsor was negligent in obtaining or maintaining FDA approval, the sponsor could be responsible for paying the petitioner award instead of the government, based on a percentage of a drug’s revenue during the period after the manufacturer should have known of the adverse data. If the manufacturer knowingly, recklessly, or with gross negligence withheld evidence of a drug safety problem from the FDA, the product sponsor could be responsible for treble damages, half paid to the petitioner and half to the government.

³²⁸ In fact, FCA qui tam actions have been upheld against constitutional challenge on the grounds that the government itself is the real party in interest, bearing the real injury. Rabkin, *supra* note 251, at 198.

³²⁹ *Alfred L. Snapp & Son, Inc. v. Puerto Rico ex rel. Barez*, 458 U.S. 592, 607 (1982).

J. *THE CHALLENGES OF CREATING A NEW INDUSTRY*

Observational and clinical research have highly variable costs. One can estimate the cost of this research by looking at how much the government spends to facilitate this research. For example, the NIH provides several different types of grants to directly sponsor medical research; the R series is the most common.³³⁰ The most common of the R series grants is the NIH Research Project Grant Program (“R01”), which is used to support discrete research projects. The size and duration of these awards varies by specific funding opportunity announcement (“FOA”), but they are usually awarded for one to five years, with direct costs³³¹ generally limited to \$250,000 a year.³³² The award includes salary and fringe benefits for personnel, equipment and supplies, consultant costs, and travel expenses. One NIH Center, the National Institute of General Medical Sciences (“NIGMS”), reports that the current average size of its R01 grant is approximately \$219,000 in direct costs per year.³³³ Outlier awards, however, can be well in

³³⁰ Other types of grants include career development awards (K series), research training and fellowships (T & F series), and program project/center grants (P series). *Types of Grant Programs*, NAT’L INSTS. OF HEALTH, http://grants.nih.gov/grants/funding/funding_program.htm (last updated Dec. 6, 2012). All of these grants may help to subsidize observational and clinical research. In addition, trans-NIH programs (e.g., BISTI, ESI) and resource grants (R24, R25, and X01) provide research-related support. *Id.*

³³¹ Facilities and Administrative costs are considered indirect, which may be applied for in excess of caps on direct costs. *NIH Research Project Grant Program (R01)*, NAT’L INSTS. OF HEALTH, <http://grants.nih.gov/grants/funding/r01.htm> (last updated June 5, 2012).

³³² *Id.* For an example of a FOA with costs capped at \$250,000 annually, see *NIMHD Health Disparities Research (R01)*, DEP’T OF HEALTH & HUMAN SERVS. (Apr. 12, 2011), <http://grants.nih.gov/grants/guide/rfa-files/RFA-MD-12-001.html>. For an example of an R01 FOA with \$500,000 annually plus permitted costs, see *Effects of the Social Environment on Health: Measurement, Methods and Mechanisms (R01)*, DEP’T OF HEALTH & HUMAN SERVS. (Aug. 3, 2010), <http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-11-003.html>.

³³³ *Success Rate, Percentile Ranks and Grant Budgets: Frequently Asked Questions*, NAT’L INST. OF GEN. MED. SCIS. (Mar. 1, 2010), <http://www.nigms.nih.gov/Research/Application/SuccessRateFAQs.htm>.

excess of \$1 million annually.³³⁴ On average, in 2011, the application success rate for all NIH research grants, as well as for R01 grants in particular, was 18%.³³⁵

Given that data mining has potentially modest costs, critics might argue that a bounty proceeding system over-incentivizes simply analyzing a dataset. Significant incentives are necessary, however, because of the difference between a grant and a prize.³³⁶ With a government grant, research is funded in advance. Even if the research turns out poorly, absent something like fraud, the government does not ask for its money back (although a researcher's ability to apply for future funding may be affected). Alternatively, with prize funding, researchers run the risk that they may receive no compensation for work they have already completed. In this way, the research is akin to what Mark Lemley and Carl Shapiro have termed "probabilistic patent" rights.³³⁷ Given the inherent uniqueness of an FDA determination, uncertainty about the commercial significance of drug safety data mining research is unavoidable.

A second challenge would be how to protect the pharmaceutical industry from petitioners

³³⁴ See, e.g., Peter Reuell, *Funding Innovation: Harvard Researchers Receive \$15 Million in NIH Grants*, HARV. GAZETTE (Sept. 28, 2011), <http://news.harvard.edu/gazette/story/2011/09/funding-innovation/>.

³³⁵ Jocelyn Kaiser, *NIH Examines What Drove Its Grant Success Rate to a Record Low*, SCIENCEINSIDER (Jan. 20, 2012, 5:25 PM), <http://news.sciencemag.org/scienceinsider/2012/01/nih-examines-what-drove-its-grant.html/>. The NIH Exploratory/Developmental Research Grant Awards (R21) is another R series grant, which encourages new research projects by providing support for the early stages of project development. See *Types of Grant Programs*, *supra* note 330. In these grants, the budget for direct costs may not exceed \$275,000 over a two-year period. *Id.* The NIH Small Grant Program (R03) is an R series grant used to support pilot studies, secondary analysis of existing data, etc. See *id.* Direct costs are generally up to \$50,000 per year for two years. *Id.* These grants can all apply to both observational and clinical trials, although clinical trials generally cost more.

³³⁶ See Daniel J. Hemel & Lisa Larrimore Ouellette, *Beyond the Patents-Prizes Debate*, 92 TEX. L. REV. (forthcoming 2014) (manuscript at 12–22), available at <http://ssrn.com/abstract=2245691> (discussing R&D incentivizing mechanisms including patents, prizes, grants, and tax credits).

³³⁷ Mark A. Lemley & Carl Shapiro, *Probabilistic Patents*, 19 J. ECON. PERSP. 75, 75–76 (2005).

biased to produce anti-industry findings. Ultimately, the best safeguard against biased anti-industry research will be that pharmaceutical companies are in a position to present their own evidence to contradict petitioner claims. Beyond that, policymakers could model additional safeguards after those already applicable to the pharmaceutical industry. This would primarily include requiring conflicts disclosures, which would permit consideration of motive in evaluating research results. Also, medical journals that publish third-party funded research would be free to select for higher quality and less potentially biased study designs, selecting for practices such as double-blinding and intent-to-treat statistical analysis.³³⁸ The FDA would be free to give more weight to petitioner submissions based on research they had published in high-quality, peer-reviewed medical journals.

The industry may claim conflicts disclosures are inadequate or are inadequately enforced, but this argument cuts both ways. If the pharmaceutical industry argues in favor of stronger conflict policies and disclosure requirements, it should apply to studies conducted by all researchers. The FDA might also refuse to evaluate submitted or published research that does not include accurate disclosures.

The argument that the proposed bounty system would lead to anti-industry abuses and market inefficiencies has some basis in past *qui tam* actions. In fact, relator abuses led to reforms under the Leahy-Smith America Invents Act (“AIA”), which removed standing for private

³³⁸ “The intent-to-treat principle refers to a set of criteria for the evaluation of the benefits and risks of a new therapy that essentially calls for the complete inclusion of all data from all patients randomized in the final analyses.” John M. Lachin, *Statistical Considerations in the Intent-to-Treat Principle*, 21 CONTROLLED CLINICAL TRIALS 167, 168 (2000). This type of analysis differs from common practices in trials where researchers tend to exclude various patients or patient data. *Id.* Thus, intent-to-treat analysis is more desirable because it is less likely to produce biased results. *See id.* at 169.

individuals to sue on behalf of the government for false patent marking.³³⁹ Another potential disadvantage of a bounty proceeding is that adversarial procedures often entail significant transaction costs. Furthermore, if not properly structured, third parties' incentives may not align with public health interests. In products liability, for example, private lawyers may have incentives to collect information about injury and keep it private until their cases are sufficiently developed.

Yet, as with privacy concerns, on balance these concerns with the proposed bounty proceedings do not outweigh their potential benefits. Procedural safeguards and liability for petitioners who submit frivolous claims can minimize risks to product sponsors, and any risk to industry needs to be balanced against the great potential benefits to consumers.

The bounty proceeding system proposed in this Article has the potential to substantially improve the drug regulatory process and to create an entirely new industry, much like the FCA

³³⁹ Federal law requires that patent holders give public notice that a product is under patent by marking the product or packaging with the term "patent," or its abbreviation, "pat.," followed by the relevant patent number. 35 U.S.C. § 287(a) (2006 & Supp. V 2011). False patent marking may be asserted when a patent holder is alleged to have inaccurately marked a product with an incorrect patent number, when the number does not cover the article, or when there is intent to deceive the public. 35 U.S.C. § 292(a). False marking is believed to "wrongfully quell[] competition . . . thereby causing harm to the economy of the United States." *Stauffer v. Brooks Bros., Inc.*, 619 F.3d 1321, 1324 (Fed. Cir. 2010) (internal quotation marks omitted). The penalty for false marking is a fine of up to \$500 per offense. 35 U.S.C. § 292(a); *see Forest Grp., Inc. v. Bon Tool Co.*, 590 F.3d 1295, 1304 (Fed. Cir. 2009) (holding that the fine is \$500 per article rather than per offense). Before the AIA, anyone could bring a qui tam action to sue for the penalty and share in half of the judgment with the government. 35 U.S.C. § 292(b) (2006) (repealed 2011); *see Brooks Bros., Inc.*, 619 F.3d at 1325 (holding that anyone may qualify as a relator). This created a "cottage industry of false marking litigation." *See Forest Grp., Inc.*, 590 F.3d at 1303 (internal quotation marks omitted). However, Congress recognized that this qui tam regime created inefficiencies and significant costs to industry and limited relators' ability to sue through the AIA. *See Brooks v. Dunlop Mfg. Inc.*, 702 F.3d 624, 629 (Fed. Cir. 2012) (discussing legislative history). Now, only parties that have suffered a competitive injury can bring an action for false marking. Moreover, marking a product with an expired patent number is no longer actionable. *Compare* 35 U.S.C. § 292(b) (2006 & Supp. V 2011) *with* 35 U.S.C. § 292(b) (2006) (repealed 2011).

has done. If financial incentives are adequate, it may even incentivize researchers to go beyond data mining HIEs. Because RCTs are the strongest evidence of a causal connection, researchers may have sufficient incentives to conduct their own clinical trials. Universities tend to conduct both data mining and clinical trials, and insofar as awards accrue to universities, education and scientific inquiry will generally benefit from the proposed system.³⁴⁰

K. A VIOXX HYPOTHETICAL

A hypothetical example will more concretely show how the pharmacovigilance system proposed in this Article would work in practice. The economic analysis provided here is easier to see in hindsight than it would be to arrive at in a real time FDA proceeding.

Vioxx is a natural choice for a hypothetical because it is prominent in the pharmacovigilance debates and because substantial litigation and research data is available. Before turning to award calculations, however, it is worth mentioning that if this system had been in place, Vioxx might never have made it to the market. Merck might have calculated its liability under this system and determined that it no longer made financial sense to market a drug it suspected was unreasonably dangerous. Alternatively, the drug might have been removed from the market sooner since this system should have resulted in a faster independent inquiry. That would have been particularly likely had researchers been able to analyze aggregated HIE data, but, of course, this data did not yet exist.

Merck conducted the initial studies that found Vioxx might cause an increased risk of cardiovascular events. In 1998, a study of 978 patients, “Study ‘090,” found a six-fold increase

³⁴⁰ While universities do have their own legal departments, it is unclear to what extent they would be likely to file bounty proceedings independently. Universities would most likely partner with law firms for representation.

in the risk of serious cardiovascular events in patients taking Vioxx.³⁴¹ Merck argued to the FDA that the relatively small number of participants did not permit conclusions about cardiovascular risk.³⁴² The VIGOR trial, discussed earlier, was a larger randomized trial sponsored by Merck. It found a five-fold³⁴³ increase in heart attack risks between patients taking Vioxx and those taking naproxen.³⁴⁴ Once again, Merck successfully argued to the FDA that the between-group difference was due to naproxen's protective effects rather than to Vioxx's adverse effects.³⁴⁵

Had these or any other Merck sponsored studies been grounds for removing Vioxx from the market, Merck would have faced no bounty proceeding liability. Merck did not directly conduct the VIGOR study, researchers at Mount Sinai Hospital and the University Health Network conducted it. However, because it was industry funded, under the proposed bounty system Merck would have the right to submit the information directly to the FDA and prevent collaborators from filing bounty proceedings. In submitting this data, Merck would only have a responsibility to submit accurate data and good faith analyses. Merck would be free to argue that Vioxx was not responsible for the increased incidence of cardiovascular events. As long as the data accurately revealed the increased risk, Merck could argue, as it did, that between-group differences had been due to the protective effects of naproxen. However, with a potential for bounty proceeding liability, it would only be in Merck's best financial interests to make this claim if it were legitimately convinced that the claim were accurate. By leaving the drug on the market, the company would open itself up to liability once better evidence was available from

³⁴¹ PICHEREAU, *supra* note 116, at 3.

³⁴² *Id.* at 4.

³⁴³ Jüni et al., *supra* note 121, at 2021. The VIGOR study reports this as a four-fold difference, but subsequent analysis found this was inaccurate. *See id.* at 2027.

³⁴⁴ Claire Bombardier et al., *Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*, 343 NEW ENG. J. MED. 1520, 1525–27 (2000).

³⁴⁵ Waxman, *supra* note 103, at 2577.

other sources.

What evidence would have provided the basis for an adverse FDA determination? This is a difficult question to answer. Merck reported the decision to remove the drug was based on the three-year results of its own research, namely the (then) unpublished Adenomatous Polyp Prevention on Vioxx (“APPROVe”) study.³⁴⁶ However, this claim is suspect because it was a fairly small trial that was designed for a different purpose.³⁴⁷ Years before Vioxx’s withdrawal, insurers “including Kaiser Permanente, Group Health, Premera Blue Cross in Washington and the Veterans Administration” (“VA”) had restricted access to the drug.³⁴⁸ Group Health reported it harbored safety concerns from the time of Vioxx’s release “based on unpublished data on the FDA Web site.”³⁴⁹ The VA became aware of Vioxx’s risks from data mining its own EMR system, the Veterans Health Information Systems and Technology Architecture.³⁵⁰ The VA subsequently limited the use of Vioxx to patients who had no other alternatives and required careful monitoring of these patients.³⁵¹

A meta-analysis published in *The Lancet* in 2005 identified 18 RCTs and 11 observational studies that had published data on Vioxx’s risks.³⁵² It noted that the risk of heart attack was evident from 2000 onwards based on published data³⁵³ and that both the manufacturer

³⁴⁶ Letter from William F. Keane, Vice President, US Med. & Scientific Affairs, Merck & Co., Inc., to Healthcare Professional (2004), *available at* <http://www.pbm.va.gov/vacenterformedicationsafety/vioxx/Physiciannotificationletter.pdf>.

³⁴⁷ *Vioxx: An Unequal Partnership Between Safety and Efficacy*, 364 LANCET 1287, 1287 (2004).

³⁴⁸ *Some Insurers Limited Vioxx*, *supra* note 227.

³⁴⁹ *Id.* (quoting Marc Mora, Chairman, Pharm. & Therapeutics Comm., Group Health).

³⁵⁰ FRED TROTTER & DAVID UHLMAN, *HACKING HEALTHCARE* 2 (2013).

³⁵¹ *See id.*

³⁵² Jüni et al., *supra* note 121, at 2022–23.

³⁵³ *Id.* at 2021, 2025.

and the FDA should have withdrawn the drug several years earlier.³⁵⁴ Merck claimed that the APPROVe study only demonstrated risk with long-term use and that there was no excess risk in the first 18 months.³⁵⁵ However, this claim was not accurate: the publically available data established that patients were at risk within a few months.³⁵⁶

Had the proposed system been in place, any of the parties that conducted these RCTs, observational studies, or even meta-analyses could file a bounty proceeding and claim to be a petitioner. If the field seems crowded, Vioxx's exceptional position in the pharmaceutical market and the widespread concern about its cardiovascular risk resulted in an unusual amount of research. Moreover, not every researcher could actually qualify as a petitioner. Some of the studies were small and of poor quality. Only the researchers who produced evidence that was material to an FDA withdrawal determination could qualify. In the event that multiple researchers were found to have contributed materially to a determination, the award could have been split between them at the FDA's discretion.

Let us take the hypothetical case in which one or more petitioners filed a bounty proceeding, and on the basis of that submission, Vioxx was withdrawn from the market. An award to those petitioners would be paid based on the calculated savings for the government over a particular time period due to the withdrawal. For purposes of this example, we will use a five-

³⁵⁴ *Id.* at 2021.

³⁵⁵ Letter from William F. Keane, *supra* note 346. Two earlier meta-analyses by Merck claimed no evidence of a rise in cardiovascular risk, Alise S. Reicin et al., *Comparison of Cardiovascular Thrombotic Events in Patients with Osteoarthritis Treated with Rofecoxib Versus Nonselective Nonsteroidal Anti-inflammatory Drugs (Ibuprofen, Diclofenac, and Nabumetone)*, 89 AM. J. CARDIOLOGY 204 (2002), or of a risk when compared with naproxen, Marvin A. Konstam et al., *Cardiovascular Thrombotic Events in Controlled, Clinical Trials of Rofecoxib*, 104 CIRCULATION 2280 (2001).

³⁵⁶ Jüni et al., *supra* note 121, at 2025.

year time frame.³⁵⁷

Calculating savings to the government is relatively complicated and differs from calculating patient injury. Patient injury may take into account non-economic injuries, such as pain and suffering, and economic injuries, such as lost wages, that are not direct costs to the government. Patient injuries have indirect and uncertain costs to the government. For example, consider lost wages: the government may lose tax revenue from lost wages because of Vioxx related injuries, but, on the other hand, Vioxx's *removal* has been calculated to have resulted in \$19 billion in lost wages from decreased productivity from individuals with joint conditions.³⁵⁸ Even smoking, widely regarded as a major drain on health care resources, may ultimately result in cost savings to the government.³⁵⁹ Nonsmokers live longer and incur more health care costs at advanced ages after they have left the workforce.³⁶⁰

For ineffective medicine, the government's direct savings would be the cost paid for a drug minus the cost of alternative therapy. It is hard to know what patients would have taken if Vioxx had not been available. Assuming that most patients would have turned to another pharmaceutical intervention, one option would be non-selective NSAIDs such as naproxen—the comparator drug in the VIGOR study. Naproxen retails for approximately \$0.06 per pill, while Vioxx had cost about \$3.00 per pill.³⁶¹ Alternatively, patients might have taken another COX-2

³⁵⁷ Here, a five-year time frame was chosen to correlate with the time period Vioxx was on the market. The optimal time frame over which awards would be calculated may vary on a case-by-case basis, or adhere to a standard to be determined.

³⁵⁸ This was calculated as the cost in the first year alone. Craig L. Garthwaite, *The Economic Benefits of Pharmaceutical Innovations: The Case of Cox-2 Inhibitors*, 4 AM. ECON. J.: APPLIED ECON. 116, 118 (2012).

³⁵⁹ Jan J. Barendregt et al., *The Health Care Costs of Smoking*, 337 NEW. ENG. J. MED. 1052 (1997).

³⁶⁰ *Id.* at 1052.

³⁶¹ *Current Lawsuits: Vioxx*, PRESCRIPTION ACCESS LITIG.,

inhibitor. At the time Vioxx was being sold, two other comparably priced COX-2 inhibitors were on the market: Celebrex and Bextra. After Vioxx's withdrawal, Celebrex and Bextra use also fell due to concerns that cardiovascular risk was inherent in the entire class of medications.³⁶² Shockingly, on February 18, 2005, an FDA panel voted not only to keep Celebrex and Bextra on the market, but also to allow Merck to resume Vioxx sales.³⁶³ The committee did, however, unanimously note that all three drugs "significantly increase the risk of cardiovascular events."³⁶⁴ Vioxx did not return to the market, and the FDA later reversed course and requested Bextra's withdrawal.³⁶⁵ Pfizer complied with that request on April 7, 2005.³⁶⁶ Celebrex is still an approved drug.

The problem with Vioxx was not that it was ineffective, but rather that it caused excessive adverse events. To calculate Vioxx's cost to the government, the number of excess adverse events should be multiplied by each event's cost. Estimates vary as to the extent of injury that Vioxx caused between 1999 and 2004. However, the Merck Settlement Agreement notes that approximately 29,000 potentially eligible claimants nationwide alleged heart attacks from Vioxx use and 17,000 alleged strokes.³⁶⁷ The estimated average costs to Medicare of

http://www.prescriptionaccess.org/lawsuitssettlements/current_lawsuits?id=0028 (last visited Aug. 24, 2013).

³⁶² Garthwaite, *supra* note 358, at 119.

³⁶³ What is even more shocking is that 10 of the 32 voting members of the committee "had financial conflicts of interest with at least one of the pharmaceutical companies that had drugs under examination." BIDDLE, *supra* note 122, at 29. Of the 22 non-conflicted members, only 8 voted to reinstate Vioxx's market approval, while 9 out of 10 of the conflicted members voted to put Vioxx back on the market. *Id.* Had the conflicted members abstained from voting, the committee recommendation would have been to maintain withdrawal. *Id.*

³⁶⁴ PICHEREAU, *supra* note 116, at 4 (internal quotation marks omitted).

³⁶⁵ Garthwaite, *supra* note 358, at 119.

³⁶⁶ *Id.*

³⁶⁷ Description of Settlement Agreement Between Merck & Co. and Negotiating Plaintiffs' Counsel 5, *available at*

treating a patient for 180 days after a heart attack or stroke are \$16,845 and \$16,280 respectively.³⁶⁸ This suggests that the total direct costs for patients from Vioxx use were \$765 million. Likely, that estimate is oversimplified as it only takes into account costs within the first 180 days of an event. In addition, not everyone has Medicare. That last fact is crucial for determining the award's amount, as it would only apply to patients insured by the government. About 95 million Americans, or 31% of the population, are covered by government health insurance.³⁶⁹ In our hypothetical example, assume that the cost of caring for someone with Medicare was about the same as with other types of government insurance. Then, 31% of \$765 million, or \$237 million, is the amount the federal government would have to pay as a result of

http://hosted.ap.org/specials/interactives/_documents/vioxx_settlement_description.pdf (last visited Aug. 24, 2013). To be an eligible claimant, a plaintiff must have filed a Vioxx lawsuit claiming heart attack, stroke, or sudden cardiac death as a result of a Vioxx ingestion. *Id.* at 1. Medical records must confirm the adverse event, medical or pharmacy records must establish the Claimant received at least 30 Vioxx pills within 60 days prior to the injury, and records must confirm Vioxx was being used within 14 days of the event. *Id.* at 2.

³⁶⁸ Elizabeth M. Sloss et al., *Direct Medical Costs Attributable to Acute Myocardial Infarction and Ischemic Stroke in Cohorts with Atherosclerotic Conditions*, 18 CEREbroVASCULAR DISEASES 8, 11–12 (2004).

³⁶⁹ “In 2004, the United States spent \$1.9 trillion, or 16 percent of its gross domestic product (GDP) on health care.” Mark W. Stanton, *The High Concentration of U.S. Health Care Expenditures*, RES. ACTION, June 2006, at 1, available at <http://www.ahrq.gov/research/findings/factsheets/costs/expriach/expendria.pdf>. Over 20% of the federal budget goes toward Medicare, which covers about 44 million Americans (37 million elderly, 6.6 million disabled), and Medicaid, which covers 48.6 million. Emily Smith & Caitlin Stark, *By the Numbers: Health Insurance*, CNN (June 28, 2012, 5:02 PM), <http://www.cnn.com/2012/06/27/politics/btn-health-care/index.html>. The federal government also covers 8 million through the Veteran's Administration. WESTAT, NATIONAL SURVEY OF VETERANS, ACTIVE DUTY SERVICE MEMBERS, DEMOBILIZED NATIONAL GUARD AND RESERVE MEMBERS, FAMILY MEMBERS, AND SURVIVING SPOUSES 123 (2010), available at <http://www.va.gov/VETDATA/docs/SurveysAndStudies/NVSSurveyFinalWeightedReport.pdf>. TRICARE covers 5.5 million military members and their dependents and the Indian Health Service covers 1.5 million Native Americans. FURROW ET AL., *supra* note 11, at 767. Under ACA, the percentage of Americans insured by the government is going to increase substantially; another 32 million will receive coverage under Medicaid alone. Abbott, *supra* note 169, at 43. A disproportionately high percentage of Vioxx claimants probably had Medicare, as heart attack and stroke are both more prevalent in elderly populations (Vioxx's primary customers).

adverse effects from Vioxx during its market life.³⁷⁰

It further complicates this estimate to consider Vioxx's possible benefits resulting in cost savings. These benefits include GI hemorrhages in patients that would otherwise be taking non-selective NSAIDs. Yet, a meta-analysis has found exposure to Vioxx was associated with a higher adjusted odds ratio for GI hemorrhage (4.28) than for non-selective NSAIDs (2.38), which means that Vioxx may not have even decreased the risk of gastrointestinal side effects.³⁷¹

Two hundred and thirty-seven million dollars may not seem substantial, particularly since Merck paid \$4.85 billion to settle its tort claims. However, remember that this award determination, paid by the federal government, assumes that Merck acted with reasonable care. It is neither designed to punish product sponsors, nor to compensate patients, who still have access to the tort system. This amount should, however, be adequate to motivate third parties to

³⁷⁰ In the Vioxx litigation, a group of private insurers and health plans asserted independent claims for economic injury against Merck, which settled for \$80 million. *In re Vioxx Prods. Liab. Litig.*, 869 F. Supp. 2d 719, 722 (E.D. La. 2012). The bounty proceeding system proposed in this example would base an award prospectively on how much the government would save in the 5 years *following* withdrawal (as opposed to the 5 years and 4.5 months that Vioxx was on the market). That would be a more challenging number to project, depending on how many additional factors were taken into account. The number would likely be larger than for the preceding five years because Vioxx use grew during most of its market life until enough published data had accumulated demonstrating increased cardiovascular risk. The difference between the prospective and retrospective calculation may be accounted for by including costs from the first 4.5 months Vioxx was on the market. Many of these figures are subject to debate, and in a bounty proceeding, the FDA, as finder of fact, would be responsible for making a determination as to which is most accurate.

³⁷¹ Rhema Vaithianathan et al., *Iatrogenic Effects of COX-2 Inhibitors in the US Population: Findings from the Medical Expenditure Panel Survey*, 32 DRUG SAFETY 335 (2009). On the other hand, studies have found GI benefits from the use of Vioxx versus non-selective NSAIDs. See, e.g., Y.F. Chen et al., *Cyclooxygenase-2 Selective Non-steroidal Anti-inflammatory Drugs (Etodolac, Meloxicam, Celecoxib, Rofecoxib, Etoricoxib, Valdecoxib and Lumiracoxib) for Osteoarthritis and Rheumatoid Arthritis: A Systematic Review and Economic Evaluation*, 12 HEALTH TECH. ASSESSMENT, April 2008, at 1. Another study also found no increase in GI side effects after the withdrawal of Vioxx. Chirs Metcalfe et al., *International Regulatory Activity Restricting COX-2 Inhibitor Use and Deaths Due to Gastrointestinal Haemorrhage and Myocardial Infarction*, 19 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 778 (2010).

independently research Vioxx's effects and submit the data to the FDA.

The hypothetical does not end here. Under the proposed system, the adverse determination gives way to a right of discovery. Plaintiffs' lawyers worked quickly in the Vioxx litigation and uncovered a substantial body of incriminating internal company communications. On this basis, it seems reasonable that the FDA would determine Merck was negligent and even that it acted willfully. But, there is no guarantee that this would have occurred. In fact, during the Vioxx litigation, the multi-district litigation held six bellwether trials, and only one resulted in a verdict for the plaintiffs.³⁷²

Assuming negligence was found, Merck would pay the award, and the award would be calculated based on drug revenue. In contrast to government costs, Vioxx's revenue is far simpler to calculate. Vioxx revenue was about \$330 million in 1999,³⁷³ \$2 billion in 2000,³⁷⁴ \$2.5 billion in 2002 and 2003,³⁷⁵ and \$1.3 billion in 2004.³⁷⁶ That means Vioxx earned approximately \$8.6 billion during its market lifecycle.³⁷⁷ The award would therefore be \$8.6 billion if the FDA determined that Merck acted negligently in getting the drug approved on the basis of its submitted research. If the FDA determined that Merck should only have known the drug was unsafe since 2000 (the Lancet meta-analysis' conclusion), only the revenue since 2000—\$8.3 billion—would be the basis for an award. A later date would similarly reduce the

³⁷² *In re Vioxx Prods. Liab. Litig.*, 869 F. Supp. 2d at 721 & n.2. Additional bellwether trials were held in state courts. *See id.*

³⁷³ Melody Petersen, *Increased Spending on Drugs Is Linked to More Advertising*, N.Y. TIMES (Nov. 21, 2001), <http://www.nytimes.com/2001/11/21/business/increased-spending-on-drugs-is-linked-to-more-advertising.html>.

³⁷⁴ Rotthoff, *supra* note 108, at 1868.

³⁷⁵ HELLER & LAVALLEE, *supra* note 116, at 5.

³⁷⁶ Associated Press, *Merck to Fund \$4.85B Vioxx Settlement*, CBS NEWS (Feb. 11, 2009, 2:37 PM), http://www.cbsnews.com/2100-500395_162-4269301.html.

³⁷⁷ It had profit margins of about 80%. Rotthoff, *supra* note 108, at 1874.

award. In the event Merck was found to have knowingly, recklessly, or with gross negligence caused an unsafe product to have been approved (or to have remained on the market), the company would be responsible for treble damages. Such a determination seems reasonable in light of the communications discovered between Merck executives. That determination would result in an award of near \$26 *billion*. Half of this payment would be awarded to the federal government. That sum is not unreasonable. In fact, it is less than the amount many commentators had predicted for Vioxx's tort liability.³⁷⁸ To the extent it does seem large, Vioxx was an unusually strong revenue generator.³⁷⁹

III. CONCLUDING THOUGHTS

The public would benefit from reforming the current industry-oriented system of post-market drug regulation into a more consumer-oriented system. Policymakers should create an administrative bounty proceeding to incentivize third parties to submit evidence to the FDA contesting an approved drug's safety and efficacy. The federal government should pay petitioners awards based on the estimated savings the federal government would experience from not paying for ineffective and dangerous treatments. Product sponsors should have to pay petitioners awards if they fail to appropriately monitor their own products (to the extent they are found negligent or worse). This proposal does not seek to replace existing regulatory mechanisms, in which the FDA, product sponsors, and third parties all play indispensable roles.

Widespread access to aggregated data from HIEs is the means and catalyst for this change. This data will allow the FDA, product sponsors, and third parties to perform effective

³⁷⁸ *Merck's Vioxx Liability Could Reach \$38 Billion*, FORBES.COM (Dec. 3, 2004, 2:31 PM), <http://www.forbes.com/2004/12/03/1203automarketscan13.html/>.

³⁷⁹ HOLLY PRESLEY, INSTITUTIONS IN CRISIS: VIOXX AND THE MERCK TEAM EFFORT 10 (2009), available at <http://www.duke.edu/web/kenanethics/CaseStudies/Vioxx.pdf> ("Such a large number of patients ensured that sales revenue would be among the highest in recent history.").

post-market risk assessment. To some extent, these parties can accomplish this under existing frameworks. For example, HIEs are already able to incorporate data fields useful for pharmacovigilance, aggregate data, and make this information available to the FDA and other stakeholders. However, for this to occur efficiently, stakeholders should be cognizant that HIEs are rich resources for pharmacovigilance. Because HIEs may elect to restrict access to their data, they should be aware that granting product sponsors and third parties access will result in public benefits. More ambitiously, to alter the fundamentally lopsided nature of the risk-assessment process, this Article proposes creation of a new administrative bounty proceeding.

Opposition to this proposal may come from the pharmaceutical industry, as well as from parties who are philosophically opposed to what they may characterize as another layer of government bureaucracy. On the other hand, product sponsors may prefer a third-party enforcement model because it may act as an early warning system that could limit their tort liability. Also, a decentralized mechanism may be more efficient and less wasteful than additional subsidization of the FDA or other agencies. In short, an administrative bounty proceeding has the potential to lead to business improvements, government savings, and better consumer outcomes. These benefits, both human and financial, should be enough to generate a base of support for this Article's proposal.