

# COLLAPSING THE DISTINCTION BETWEEN EXPERIMENTATION AND TREATMENT IN THE REGULATION OF NEW DRUGS

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*The explosion of scientific knowledge in recent decades has simultaneously increased pressure on the Food and Drug Administration (FDA) both to expedite market entry of promising medical breakthroughs and to safeguard the public from harms caused by new products. Ironically, as the FDA and drug manufacturers spend huge sums in the premarketing phase gathering and interpreting data from planned trials, an enormous amount of valuable information about postmarketing clinical experiences with FDA-regulated drugs is not being effectively captured. The Article asserts that the FDA should formally recognize the blurred line between experimentation and treatment by adopting a more fluid approach to its review of new medical technologies. It argues that the FDA should shift its focus toward harnessing and distilling accumulated experiential knowledge about the effects of new drugs so as to enable patients and doctors to make rational treatment decisions based on inevitably imperfect information. The Article sets forth an alternative regulatory approach that seamlessly incorporates prospective outcomes data into the FDA drug review process. This approach would be facilitated by the creation of a centralized database that serves as a clearinghouse of information about treatment outcomes. The proposed scheme would help to address current failures in the implementation of the agency's "fast-track" programs. More broadly, it could serve as the instrumentality to effectuate a shift in the perceived role of the FDA from market gatekeeper to consolidator and purveyor of information about drug safety and efficacy.*

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## I. INTRODUCTION

“Where to elect there is but one,  
 ‘Tis Hobson's choice; take that or none.”<sup>1</sup>

The debate over the regulation of new drugs has historically focused on the extent to which the Food and Drug Administration (FDA) should be able to mandate data production and the proper limits of agency authority over the information that is generated about drug safety and efficacy. Regardless of their views on the relative merits of government intervention versus patient and physician autonomy, most analyses start from the presumption that the randomized controlled trial (RCT) is the “gold standard” for biomedical research.<sup>2</sup> The question then turns on the point at which the benefits of such experimentation are outweighed by its social costs, including drags on innovation, reduced access to promising medical breakthroughs, and higher pharmaceutical prices. This Article challenges the notion that the results of RCT should dictate the market for new drugs. It highlights the deficiencies of the current scheme and outlines an alternative

1. THOMAS WARD, ENGLAND'S REFORMATION 373 (D. & J. Sadlier & Co. 1853) (1710). See Webster's Online Dictionary, <http://www.websters-online-dictionary.org/Ho/Hobson%2527s+choice.html> (last visited Jan. 13, 2011).

2. Jennifer Kulynych, *Will FDA Relinquish the “Gold Standard” for New Drug Approval? Redefining “Substantial Evidence” in the FDA Modernization Act of 1997*, 54 FOOD & DRUG L.J. 127, 132 (1999). See also ROBERT J. LEVINE, ETHICS AND REGULATION OF CLINICAL RESEARCH 211 (1988); Lars Noah, *Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy*, 28 AM. J.L. & MED. 361, 392 (2002); Steven M. Teutsch et al., *Comparative Effectiveness: Asking the Right Questions, Choosing the Right Method*, 24 HEALTH AFF. 128, 128 (2005).

regulatory path in which RCT plays an important, but not determinative, role in supplying evidence about drug safety and efficacy.

This Article asserts that the FDA should formally recognize the blurred line between experimentation and treatment by adopting a more fluid approach to its review of new medical technologies. In order to effectuate this change, the agency's assumed role should shift from gatekeeper of promising new medical products to facilitator of consolidation and dissemination of information about those products. While this principle should apply across product sectors, this Article will present specific proposals for the regulation of drugs.

Part II provides an historical overview of the Federal Food, Drug and Cosmetic Act (FDACA), highlighting the co-evolution of the modern regulatory regime with the advent of the RCT as the centerpiece of biomedical research. This Part discusses physician resistance to the RCT-centered approach and recent reforms to address escalating drug development costs resulting from the contemporary regulatory paradigm. Part III explains how market incentives and political pressures lead to information production and disclosure that is suboptimal from a public goods perspective. It also discusses the inherent limitations of RCT and untapped opportunities to supplement the data generated by designed trials with information derived from the treatment setting.

Part IV recounts past proposals and adopted measures to address the problem of suboptimal information on the effects of new drugs. Part V sets forth an alternative regulatory scheme of earlier market entry coupled with prospective postmarketing surveillance via a centralized database serving as a clearinghouse for experiential data. It also delineates and responds to anticipated criticisms of the proposed regime. Part VI concludes by summarizing core findings and recommendations.

## II. HISTORICAL EVOLUTION OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT

### *A. The Advent of the Modern Regulatory Scheme*

The first major federal law governing therapeutic drugs, the 1906 Food and Drugs Act,<sup>3</sup> granted the FDA authority to penalize manufacturers for marketing adulterated or misbranded drugs.<sup>4</sup> The 1912 Sherley Amendment revised the definition of "misbranded" to include knowingly false statements about a drug's therapeutic effects.<sup>5</sup> However, the FDA

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3. Ch. 3915, 34 Stat. 768 (1907).

4. Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1758 (1996).

5. *Id.* at 1760-61.

had no power to demand, prior to marketing, any evidence that a drug was safe or would perform as the seller claimed.

The 1938 Federal Food, Drug, and Cosmetic Act (FD&C Act) was enacted in response to the infamous “Elixir Sulfanilamide” disaster in which over one hundred Tennessee residents were poisoned by an untested potion.<sup>6</sup> It mandated drug manufacturers to notify the FDA prior to marketing any new drug so as to give the FDA time to evaluate its safety.<sup>7</sup> Although the 1938 Act did not empower the FDA to evaluate the efficacy of new drugs, the law eliminated the knowledge qualifier by defining “misbranded” as “false or misleading in any particular.”<sup>8</sup> “This meant that the seller’s state of mind, i.e., the possible genuineness of his belief in claims that might not be scientifically supportable, was no longer relevant. The legal test became: Would the product in fact work as its label claimed?”<sup>9</sup>

Since the FDA had no means to formally assess efficacy, this presented thorny questions about the agency’s ability to determine that claims were false or misleading. Congress attempted to resolve this dilemma by adding a provision to the Act, which imposed on sellers an obligation to disclose negative expert opinions about the drug.<sup>10</sup> “Under this language, the draftsmen believed, it would be appropriate to hold a drug misbranded, even though some experts testified that it would work as claimed, if the label failed to disclose that most experts believed it would not.”<sup>11</sup> Although the FDA’s authority was limited to reviewing the safety of new drugs, as a practical matter, the agency was compelled to consider therapeutic effectiveness as well. Whether a drug was “safe,” after all, depended on whether the drug’s benefits outweighed its risks.<sup>12</sup>

The modern U.S. drug regulatory system was born in 1962 with passage of the Kefauver–Harris Amendments.<sup>13</sup> The thalidomide tragedy in the early 1960s prompted legislators to transform what had been a languishing bill on pharmaceutical price controls into a fundamental overhaul of the regulatory regime.<sup>14</sup> The 1962 Amendments replaced the existing premarket *notification* system with a premarket *approval* system.<sup>15</sup> Whereas before drug manufacturers were permitted to market their drugs after

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6. *Id.* at 1764.

7. *Id.* at 1761–62. The Act also introduced the prescription-only regulation, which had the effect of shifting ultimate responsibility to make informed treatment decisions from patients to physicians. Ariel Katz, *Pharmaceutical Lemons: Innovation and Regulation in the Drug Industry*, 14 MICH. TELECOMM. & TECH. L. REV. 1, 27 (2007).

8. Federal Food, Drug, and Cosmetic Act § 502(a), ch. 675, 52 Stat. 1040, 1050 (1938) (codified as amended at 21 U.S.C. § 352(a) (2006)); Merrill, *supra* note 4, at 1762.

9. Merrill, *supra* note 4, at 1762.

10. *Id.* at 1763.

11. *Id.*

12. *Id.* at 1764.

13. *Id.*

14. Kulynych, *supra* note 2, at 132.

15. Merrill, *supra* note 4, at 1764–65.

a statutorily prescribed 180 day waiting period unless the FDA challenged their safety, drug makers were now prohibited from selling new drugs until the agency was sufficiently convinced of their safety and efficacy.<sup>16</sup>

In addition to submitting “adequate tests” demonstrating safety, drug sponsors were required to provide “substantial evidence” of effectiveness, defined as “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified . . . to evaluate the effectiveness of the drug involved.”<sup>17</sup> The agency implemented its statutory mandate with an elaborate regulatory scheme comprising preclinical animal testing followed by three premarketing phases of human clinical trials.<sup>18</sup> In 1970, the FDA promulgated regulations which outlined the key features of clinical trials that drug makers must undertake.<sup>19</sup> The regulations mandated that the study incorporate a control, presumptively a placebo control, and meet other rigorous scientific standards.<sup>20</sup> Although the FDA maintains that the quantum of evidence required to demonstrate efficacy is discretionary, as a practical matter, the agency typically requires two successful RCTs for new drug approval.<sup>21</sup>

The historical evolution of the contemporary regulatory framework for new drugs is closely linked to the advent of the RCT as the “gold standard” of biomedical research.<sup>22</sup> Prior to the introduction of the RCT in the mid-twentieth century, medical research was based primarily on the anecdotal information gleaned from clinicians whose primary intent was to treat the immediate patient.<sup>23</sup> Although FDA regulations promulgated in

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16. Drug Amendments of 1962, Pub. L. No. 87-781, § 102, 76 Stat. 780, 781 (codified as amended at 21 U.S.C. § 355(d) (2006)); Merrill, *supra* note 4, at 1765.

17. § 102, 76 Stat. at 781.

18. See 21 C.F.R. § 312.21 (2009); *Clinical Trial Phases*, NAT'L LIBR. OF MED., <http://www.nlm.nih.gov/services/ctphases.html> (last updated Apr. 18, 2008) (describing clinical trials phases). Results from Phase III trials are the primary basis of the FDA's risk-benefit analysis of the drug under review. Barbara A. Noah, *Adverse Drug Reactions: Harnessing Experiential Data to Promote Patient Welfare*, 49 CATH. U. L. REV. 449, 458 (2000). If the potential benefits to the target patient population outweigh the risks of side effects for some patients, the FDA will approve the drug for marketing. *Id.*

19. 21 C.F.R. § 314.126 (2009).

20. *Id.*

21. Kulynych, *supra* note 2, at 130. The Food and Drug Administration Modernization Act (FDAMA) of 1997 relaxed the “substantial evidence” standard to allow the FDA to approve a drug application based on one instead of two RCTs demonstrating efficacy. FDAMA § 115, Pub. L. 105-115, 111 Stat. 2296 (1997) (codified as amended at 21 U.S.C. § 355(d) (2006)). Section 115 of the FDAMA permits, but does not mandate, the FDA to approve drugs based on data from one adequate and well-controlled clinical trial and confirmatory evidence (e.g., peer-reviewed published research or related pharmacokinetic and pharmacodynamic studies) demonstrating efficacy. *Id.* However, the agency generally interprets “substantial evidence” to require two well-controlled Phase III trials prior to market approval. See Kulynych, *supra* note 2, at 143.

22. Kulynych, *supra* note 2, at 131. See also LEVINE, *supra* note 2, at 211 (“[T]he RCT is the gold standard for evaluating therapeutic efficacy.”); Noah, *supra* note 2, at 392; Teutsch et al., *supra* note 2, at 128 (“When assessing efficacy, RCTs are considered to be the gold standard.”).

23. Noah, *supra* note 2, at 400. See also Alejandro R. Jadad & Drummond Rennie, Editorial, *The Randomized Controlled Trial Gets a Middle-aged Checkup*, 279 JAMA 319, 319 (1998); Editor's

the 1940s contained requirements to ensure the potency and purity of insulin and antibiotics, “widespread concern about the effectiveness of most pharmaceuticals did not arise until development of the RCT made scientific assessments of effectiveness possible.”<sup>24</sup>

The establishment of the effectiveness requirement stemmed from legislators’ concerns about the dangers of ineffective drugs entering the market and displacing proven remedies. Such concerns were heightened by their perception that the diffusion of medical knowledge was slow and inefficient, and therefore useless drugs could potentially be prescribed for long periods of time before the medical community was made aware of their lack of clinical utility.<sup>25</sup> The statutory parameters of the effectiveness requirement were shaped by the Congressional testimony of prominent academic scientists who extolled the virtues of controlled clinical trials. Dr. Louis Lasagna, head of the Division of Clinical Pharmacology at Johns Hopkins University, explained to Senators that a regulatory mandate for “adequate tests” conducted by “reasonable and capable scientists” was necessary to improve the poor quality of research conducted by pharmaceutical firms to support claims about new drugs.<sup>26</sup> Another leading clinical pharmacologist warned Senators that the “flooding of the market with little understood drugs” had created a public health crisis that could only be resolved by mandatory scientific evaluation of drug efficacy.<sup>27</sup>

The legislative history of the Kefauver–Harris Amendments reveals academic scientists’ consternation about physicians’ reliance on impressions and anecdotal experience to guide treatment decisions. Louis Lasagna noted that “[t]he history of medicine is, unhappily, replete with examples of useless drugs employed for years, decades, or centuries, by countless physicians before a few properly conducted experiments proved the drugs to be without value.”<sup>28</sup> In 1973 the Supreme Court rejected a challenge to the efficacy regulations adopted by the FDA under the authority granted to the agency by the 1962 Amendments.<sup>29</sup> Upholding the FDA’s

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Choice, *Fifty Years of Randomised Controlled Trials*, 317 BRIT. MED. J. (1998). The modern clinical trial first rose to prominence in medical research during World War II, “when the U.S. military undertook large-scale, systematic testing” of remedies for tuberculosis and malaria on groups of enlisted soldiers. Kulynych, *supra* note 2, at 131.

24. Kulynych, *supra* note 2, at 132.

25. See S. REP. NO. 87-1744, at 33 (1962), reprinted in 1963 U.S.C.C.A.N. 2884, 2902 (views of Sens. Kefauver, Carroll, Hart, Dodd, and Long).

26. See *Drug Industry Antitrust Act: Hearings on S. 1552 Before the Subcomm. on Antitrust and Monopoly of the S. Comm. on the Judiciary*, 87th Cong., 1st Sess. 281–82 (1961) (statement of Dr. Louis Lasagna, Head of the Division of Clinical Pharmacology, Johns Hopkins University).

27. *Id.* at 313.

28. Lars Noah, *Medicine’s Epistemology: Mapping the Haphazard Diffusion of Knowledge in the Biomedical Community*, 44 ARIZ. L. REV. 373, 435–36 n.270 (2002). See also Pharm. Mfrs. Ass’n v. Richardson, 318 F. Supp. 301, 307–08 (D. Del. 1970) (recounting similar testimony from prominent academic physicians and pharmacologists).

29. See *Weinberger v. Hynson*, 412 U.S. 609, 631 (1973).

rejection of a drug application containing only testimonial evidence from experts and physicians, the Court noted: “[S]trict and demanding standards, barring anecdotal evidence indicating that doctors ‘believe’ in the efficacy of a drug, are amply justified by the legislative history. The hearings . . . show a marked concern that impressions or beliefs of physicians, no matter how fervently held, are treacherous.”<sup>30</sup>

The fundamental changes implemented by the 1962 Amendments induced a notable shift in the FDA’s view of its consumer protection role.<sup>31</sup> The agency was granted power both to decide which drugs enter the market and to determine what information should be included in the labeling in the event that a drug is approved.<sup>32</sup> Thus, the FDA was transformed into a “warrantor of manufacturer compliance with the rules that govern drug development and marketing” and as such “is repeatedly reminded, and often reminds us, that it shares responsibility for any drug that causes harm.”<sup>33</sup>

In contrast to the stringent requirements of the preapproval period,<sup>34</sup> the FDA’s postapproval demands on drug manufacturers are relatively minor. The FDA mandates postmarketing trials as a condition for approval only in select circumstances.<sup>35</sup> The agency’s predominant focus is on the premarketing risk/benefit analysis that serves as the basis for the approval decision, with comparatively fewer resources devoted to postmarketing surveillance of the effects of new drugs.<sup>36</sup> The FDA has the power to withdraw the approval of a drug on the market,<sup>37</sup> but it rarely does so.<sup>38</sup> When a postapproval problem arises, the manufacturer and the agency generally negotiate a remedy to avoid further regulatory action. Such a remedy may include making revisions to the labeling or restricting distri-

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30. *Id.* at 618.

31. Merrill, *supra* note 4, at 1767–68.

32. Catherine T. Struve, *The FDA and the Tort System: Postmarketing Surveillance, Compensation, and the Role of Litigation*, 5 YALE J. HEALTH POL’Y L. & ETHICS 587, 594 (2005).

33. Merrill, *supra* note 4, at 1768.

34. The FDA’s expansive power to regulate new drugs lies in stark contrast to its limited authority over dietary supplements. The Dietary Supplement Health and Education Act of 1994 significantly scaled back FDA authority over these products. *See* Pub. L. No. 103-417, 108 Stat. 4325 (1994) (codified as amended in scattered sections of 21 U.S.C.). Manufacturers need not demonstrate safety prior to marketing, unless the product contains a new ingredient. *See* 21 U.S.C. § 350(b) (2006). The burden of proof is on the FDA to show that the product poses an unreasonable risk of harm before it may be withdrawn from the market. *See Id.* § 342(f)(1).

35. *See infra* pp. 41–42.

36. Struve, *supra* note 32, at 594.

37. *See* 21 U.S.C. § 355(e) (2006).

38. The FDA has used this authority only once, to withdraw the diabetes drug phenformin from the market in 1977 after it was found to cause dangerous buildup of lactic acid in the blood. U.S. GOV’T ACCOUNTABILITY OFFICE, GAO-06-402, DRUG SAFETY: IMPROVEMENT NEEDED IN FDA’S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS 10 n.19 (2006).

bution of the drug in order to minimize a significant risk associated with the drug.<sup>39</sup>

### *B. Physician Resistance to the RCT-centered Approach*

The American Medical Association (AMA) presented a notable exception to the parade of witnesses who testified at the hearings on the 1962 Amendments about the need for RCT to substantiate drug claims. AMA President Dr. Hugh H. Hussey testified in strong opposition to the efficacy requirement, arguing that drug effectiveness should be determined by the individual physician.<sup>40</sup> Significant skepticism persists within the medical community regarding the clinical utility of RCT, particularly among community practitioners unaffiliated with academic medical centers. This resistance to fully embrace RCT reflects physicians' traditional reliance on personal experience and anecdotal information to guide treatment decisions.<sup>41</sup>

Physicians have on occasion openly challenged the FDA's use of RCT to dictate labeling requirements. In the early 1970s, a group of nearly 200 physicians challenged an agency proposal to require a warning of cardiac risks associated with an oral hypoglycemic drug after a large-scale RCT suggested this problem.<sup>42</sup> Although a federal court rejected the petition as premature, the effort illustrates skepticism within the medical community about agency conclusions drawn from the results of RCT.<sup>43</sup> Decades after the RCT was adopted as the gold standard of biomedical research, many physicians remain wary of relying on RCT to guide treatment decisions. For instance, a recent *New York Times* article discussing differences of opinion about the optimal treatment for glioblastoma (a type of brain tumor) noted the fact that most physicians have made up their minds despite the absence of definitive data: "In fact, doctors are so set in their opinions on this issue that most would be unwilling to suggest that patients enter a study in which their treatment . . . would be decided at random."<sup>44</sup>

Tensions between the FDA and the medical community regarding "off-label" uses of approved drugs reveal conflicting mindsets about the

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39. *Id.* at 10.

40. *See Drug Industry Antitrust Act: Hearing on S. 1552 Before the Subcomm. on Antitrust and Monopoly of the S. Comm. on the Judiciary*, 87th Cong., 1st Sess. 36 (1961) (statement of Hugh H. Hussey, M.D., Chairman of the Bd. of Trustees, AMA).

41. Noah, *supra* note 28, at 383-84. *See also* Amy L. Wax, *Technology Assessment and the Doctor-Patient Relationship*, 82 VA. L. REV. 1641, 1648 (1996) ("[I]n actual medical practice, [treatment decisions] are often based not on accurate information but on intuition, prejudice, anecdote, or unsubstantiated lore.").

42. Noah, *supra* note 28, at 442.

43. *Id.*

44. Gina Kolata & Lawrence K. Altman, *Weighing Hope and Reality in a Cancer Battle*, N.Y. TIMES, Aug. 28, 2009, at A1.



relative importance of RCT. Once a drug has been approved for a single indication, doctors are free to prescribe that drug for any indication, irrespective of the existence of any clinical data demonstrating the drug's safety and effectiveness for the off-label use.<sup>45</sup> Even if a manufacturer is conducting clinical trials to gain FDA approval for a new use of a marketed drug, physicians may prescribe the drug for off-label uses in the treatment setting without having to abide by the study protocol or to comply with informed consent requirements.<sup>46</sup> As one physician explained, "I need permission to give a new drug to half of my patients, but not to give it to them all."<sup>47</sup>

For many successful drugs, off-label use comprises a significant portion of sales.<sup>48</sup> In fact, some observers have estimated that approximately half of all prescriptions constitute off-label uses of approved drugs.<sup>49</sup> Yet the FDA sharply curtails, to the extent allowed by the courts,<sup>50</sup> the exchange of information between manufacturers and physicians regarding off-label uses that have not been vetted through the agency's rigorous review process. This reflects agency bias towards formal RCT overseen by the FDA and skepticism about information generated outside the strict parameters adopted by the agency. After a successful First Amendment challenge to FDA constraints on the promotion of off-label uses,<sup>51</sup> the FDA revised its guidance documents to permit firms to distribute reprints of journal articles discussing off-label uses.<sup>52</sup> This policy change effectively permits firms to engage in limited marketing of unapproved uses while avoiding the risk and expense attached to clinical trials required for FDA approval.<sup>53</sup>

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45. Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 369 (2007).

46. Noah, *supra* note 2, at 399.

47. *Id.* at 399–400 (citing Richard Smithells, *Iatrogenic Hazards and Their Effects*, 51 POSTGRAD. MED. J. 39, 41 (1975)).

48. Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL'Y L. & ETHICS 717, 731 (2005).

49. See Fran Kritiz, *FDA Seeks to Add Drugs' New Uses to Labels*, WASH. POST, Mar. 29, 1994, at Z11 (citing AMA official's estimate of 40–60%).

50. See, e.g., *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998), *vacated in part*, *Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000); *Thompson v. W. States Med. Ctr.*, 535 U.S. 357 (2002) (involving First Amendment challenges to the regulatory and statutory restrictions on the promotion of off-label use of pharmaceuticals).

51. *Friedman*, 13 F. Supp. 2d 51.

52. Eisenberg, *supra* note 48, at 733–34. See also *Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices*, 63 Fed. Reg. 64,556 (Nov. 20, 1998).

53. Eisenberg, *supra* note 48, at 734. Drug companies seek to evade the FDA's constraints on promotion of off-label uses by employing Medical Science Liaisons (MSLs) to discuss such uses with clinicians. MSLs, who are often physicians and pharmacists, ostensibly provide information and educational support to clinicians by highlighting the results of clinical studies of new uses of marketed drugs. See Shirley S. Wang, *Corporate News: Drug Firms' Medical Staffs Say What Salespeople Can't*, WALL ST. J., June 26, 2009, at B3.

### C. Recent Reforms to Address Barriers to Drug Development

The elaborate regulatory scheme engendered by the 1962 Amendments has given rise to steep drug development costs. The cost to bring a prescription drug to market is estimated to range from \$800 million to \$1.7 billion, and the development time may take as long as fifteen years.<sup>54</sup> Congress has enacted a series of statutes designed to ameliorate undesirable effects of the regulatory system. These include provisions to reduce drug development timelines as well as measures to compensate for high drug development costs with back end grants of exclusivity.

The Prescription Drug User Fee Act (PDUFA) of 1992 gave the agency new resources to hire additional personnel and succeeded in greatly reducing FDA review times.<sup>55</sup> Recent data indicate that nearly all new drug applications (NDAs) are reviewed within ten months of their submission.<sup>56</sup> However, a vastly greater source of delay is the time it takes to generate the preclinical and clinical data required to obtain FDA approval.<sup>57</sup>

In 1988, in response to AIDS activists protesting long delays in bringing promising therapeutic breakthroughs to market, the FDA established the “fast-track” program for drugs treating “life-threatening and severely-debilitating illnesses.”<sup>58</sup> Under this program Phase II studies jointly designed by the FDA and the drug sponsor could potentially eliminate the requirement for Phase III trials.<sup>59</sup> The fast-track program was followed by the agency’s 1992 “accelerated approval” regulations for drugs treating “serious or life-threatening illnesses,” which allowed for market approval based on trials which demonstrated an effect on surrogate endpoints (e.g., reduction in tumor volume) linked to clinical benefits (e.g., increased can-

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54. Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 164, 166 (2003) (estimating the total cost of bringing a drug to market at \$802 million and time between start of clinical testing to market approval at 90.3 months); Jim Gilbert et al., *Rebuilding Big Pharma’s Business Model*, 21 IN VIVO: BUS. & MED. REP., Nov. 2003, at 1, available at [http://www.bain.com/bainweb/PDFs/cms/Public/rebuilding\\_big\\_pharma.pdf](http://www.bain.com/bainweb/PDFs/cms/Public/rebuilding_big_pharma.pdf) (estimating cost of discovering, developing, and launching new drugs at \$1.7 billion by factoring in costs of failed projects); Tufts Ctr. for the Study of Drug Dev., *Background: How New Drugs Move Through the Development and Approval Process* (Nov. 01, 2001), [http://cssd.tufts.edu/files/uploads/how\\_new\\_drugs\\_move.pdf](http://cssd.tufts.edu/files/uploads/how_new_drugs_move.pdf) (estimating that it takes 10 to 15 years to develop a new drug).

55. Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, 106 Stat. 4491 (1992) (codified as amended at 21 U.S.C. § 379 (2006)). Congress extended the user fee program in the Food and Drug Administration Modernization Act (FDAMA) of 1997 (PDUFA II), in 2002 (PDUFA III), and again in 2007 (PDUFA IV). FDA, Prescription Drug User Fee Act (PDUFA), available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm> (last visited Jan. 13, 2011).

56. Eisenberg, *supra* note 45, at 353.

57. *Id.*

58. Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses, 53 Fed. Reg. 41,516, 41,523 (Oct. 21, 1988).

59. *See id.* at 41,519; 21 C.F.R. § 312.82 (2009).

cer survival rate).<sup>60</sup> The fast-track and accelerated approval programs were belatedly enacted into law in the Food and Drug Modernization Act (FDAMA) of 1997, and eligible drugs were given the umbrella term “fast-track products.”<sup>61</sup>

The Orphan Drug Act of 1983<sup>62</sup> was enacted in recognition of the fact that the long, costly premarketing review process made development of drugs to treat small patient populations infeasible. The Act directs the FDA to grant seven years of exclusivity for products to treat diseases and conditions affecting fewer than 200,000 patients in the United States.<sup>63</sup> This provision supplements any existing patent protection<sup>64</sup> by prohibiting for seven years the approval of the same drug for the same condition.<sup>65</sup>

The Hatch–Waxman Act of 1984<sup>66</sup> constituted a legislative compromise between the interests of generic and pioneering drug manufacturers.<sup>67</sup> The Act “provides for patent term extensions of up to five years to [partially] compensate for some of the patent life lost during” the regulatory review process, so long as the resulting patent term “does not exceed fourteen years from the date of approval.”<sup>68</sup> It also “provided five years of [data] exclusivity for new chemical entities [NCEs] not previously approved by the FDA,” and three years of data exclusivity for making changes to previously approved products “that require conducting new clinical trials to win FDA approval.”<sup>69</sup> At the same time, the Hatch–Waxman Act facilitates generic entry following the expiration of any ex-

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60. New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58,942 (Dec. 11, 1992) [hereinafter New Drug]; 21 C.F.R. §§ 314.500–.510 (2009).

61. Eisenberg, *supra* note 45, at 376. The fast-track procedures are codified in 21 U.S.C. § 356 (2006).

62. Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983).

63. 21 U.S.C. §§ 360bb–360cc (2009).

64. Since upstream basic research is heavily subsidized by the National Institutes of Health (NIH), the need for strong patent protection is largely a product of the exorbitant costs of clinical trials. Jerome H. Reichman, *Rethinking the Role of Clinical Trial Data in International Intellectual Property Law: The Case For a Public Goods Approach*, 13 MARQ. INTELL. PROP. L. REV. 1, 41 (2009). See also Marcia Angell, *The Truth About the Drug Companies*, 45 JURIMETRICS J. 465, 467 (2005) (“The few innovative drugs usually stem from publicly-funded research done at government or university labs.”).

65. 21 U.S.C. § 360cc(a) (2009).

66. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (commonly known as the “Hatch-Waxman Act”).

67. Eisenberg, *supra* note 48, at 727.

68. Eisenberg, *supra* note 45, at 352. See also 35 U.S.C. § 156(c), (g)(1)(B) (2006).

69. Eisenberg, *supra* note 48, at 727. See 21 U.S.C. §§ 355(j)(5)(F)(ii)–(iii) (2006). In theory, the data exclusivity granted by the Hatch–Waxman Act is not as valuable as the product exclusivity gained through patent protection or the market exclusivity granted by the Orphan Drug Act because in the former case generic firms have the option to generate their own data in order to gain marketing approval for the generic drug. However, as a practical matter the exclusivity grants are functionally equivalent because the data required for market entry is prohibitively costly for generic firms who cannot recoup their expenses with the rents derived from patent protection. Eisenberg, *supra* note 48, at 727. See also Reichman, *supra* note 64, at 5; Karin Timmermans, *Monopolizing Clinical Trial Data: Implications and Trends*, 4 PLOS MED. 206–07 (2007).

clusivity period by allowing generic versions of off-patent drugs to win approval through the use of an abbreviated new drug application (ANDA) showing “bioequivalence to the previously approved product.”<sup>70</sup>

The FDAMA of 1997 included a provision for six months of exclusivity as a reward for conducting pediatric trials of drugs.<sup>71</sup> This provision was extended in the Best Pharmaceuticals for Children Act of 2002.<sup>72</sup> The exclusivity period is not contingent upon an agency finding that the drug is safe and effective in children and simply extends the term of any existing market exclusivity period held by the applicant.<sup>73</sup> It is distinct from exclusivity provisions set forth in the Orphan Drug and Hatch–Waxman Acts in that it is completely decoupled from the FDA’s decision to approve the drug to be tested, and thus recognizes the value of information generation in its own right.

On the one hand, the series of reforms delineated above reflect an acknowledgement that the extensive premarketing drug review process may impede biomedical innovation. On the other hand, however, none of the enacted reforms challenge the fundamental soundness of the modern drug regulatory regime.<sup>74</sup> PDUFA funds for additional agency resources for premarketing review serve to entrench the regulatory status quo. As one prominent commentator observed:

Congress’ passage of the Drug User Fee Act, with the support of the major manufacturers of pioneer drug products, carries an obvious irony. Rather than continuing to press for relaxation of FDA’s requirements for drug approval, the manufacturers agreed to pay extra to speed up FDA’s review of their satisfaction of those requirements.<sup>75</sup>

The exclusivity provisions serve to further entrench the existing regulatory framework centered on extensive premarketing testing by sustaining the viability of the high risk/high reward business model for pharmaceuticals.

Although the FDA’s fast-track programs hold out the promise of significantly curtailing the premarketing drug review process, in reality these programs operate at the margins and have had little impact on the estab-

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70. Eisenberg, *supra* note 48, at 727. This provision effectively permits generic firms to “free-ride” on pioneering firms’ clinical trials data to support their own drug applications. Eisenberg, *supra* note 45, at 382.

71. Pub. L. No. 105-115, 111 Stat. 2296 § 111 (1997).

72. Pub. L. No. 107-109, 115 Stat. 1408 (2002) (codified as amended in scattered provisions of Titles 21 and 42 of U.S.C.).

73. See 21 U.S.C. § 355a (2006).

74. Merrill, *supra* note 4, at 1790. Proposals to dismantle the FDA or privatize agency functions were advanced during debate on the FDAMA of 1997, but the law that was enacted preserved the FDA’s core regulatory structure. Kulynych, *supra* note 2, at 127.

75. Merrill, *supra* note 4, at 1796.

lished regulatory scheme. Fast-track programs only apply to drugs to treat illnesses deemed by the FDA to be life-threatening or seriously debilitating. Moreover, while these procedures constitute a modification to the FDA's risk/benefit calculus, they do not reflect a change in the agency's perceived (both self-perceived and outwardly perceived) role as the guarantor of patient welfare. This is problematic in light of the fact that the FDA explicitly rejected a suggestion that all drugs approved through the fast-track program include patient consent documents underscoring the heightened uncertainty about the risks and benefits of fast-track products.<sup>76</sup>

Fast-track programs have stalled because the FDA mindset persists that extensive controlled clinical testing is the gold standard and any deviations from that regime should be minimized. A recent study by the National Cancer Institute found that cancer therapies in the FDA's accelerated approval system get to market no more quickly than drugs which undergo conventional review.<sup>77</sup> The failures of the accelerated review program are largely attributed to creeping conservatism on the part of the FDA. Since the program's enactment in 1992, the agency has been increasingly unwilling to approve drugs without data from large-scale RCT.<sup>78</sup>

### III. WHY THE REGULATORY STATUS QUO IS SUBOPTIMAL

#### A. Drug Manufacturers' Incentives and Disincentives

The risk/benefit analysis for new medical products is exceedingly complex and may vary significantly between individual patients considering a particular therapy.<sup>79</sup> Good information is a prerequisite for rational decision making, as even the most competent decision makers are limited by the inputs with which they base their choices. It is therefore essential that patients and physicians obtain access to clear, accurate, and relatively complete information about the effects of new drugs.

Under the current regulatory scheme, the great majority of information about a new drug is generated by the manufacturer, which funds and manages clinical trials on the drug's effects.<sup>80</sup> However, drug developers capture only a fraction of the social value of information about safety and efficacy.<sup>81</sup> This makes it difficult to rely on private markets to generate

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76. Noah, *supra* note 2, at 396. See also New Drug, *supra* note 60, at 58,957 ("Drugs approved under these provisions are not considered experimental drugs for their approved uses.")

77. Liz Szabo, *Study: Cancer Treatments Are Not Available Any Faster*, USA TODAY, July 28, 2009, at 5D.

78. *Id.*

79. See generally Daniel R. Cahoy, *Medical Product Information Incentives and the Transparency Paradox*, 82 IND. L.J. 623 (2007).

80. See Joe Collier & Ike Iheanacho, *The Pharmaceutical Industry as an Informant*, 360 LANCET 1405 (2002).

81. Eisenberg, *supra* note 48, at 718.

credible information, as “[p]rofit-seeking firms face powerful incentives” to selectively produce and disclose information about their products.<sup>82</sup>

Drug companies are not motivated to generate the socially optimal amount of information about the effects of their drugs, because the data generated could as readily negate the commercial value of the products as enhance it.<sup>83</sup> While even negative data are socially valuable, the firm does not capture this social value because it relies on sales of the drug to recoup its investment in the information generation.<sup>84</sup> Once a drug is approved for an initial indication, firms have little incentive to invest in clinical trials of additional indications. If physicians are persuaded to utilize the drug off-label for uses other than those approved by the FDA, the most rational course for the drug manufacturer is to avoid costly trials that could potentially expose previously unrecognized harmful effects.<sup>85</sup> Manufacturer-initiated studies run the risk of increasing the company’s liability exposure by revealing previously unknown harms or confirming the existence of “a problem that, in retrospect, was suggested by earlier evidence.”<sup>86</sup> Rational firms will therefore seek to limit the range of premarketing trials required for approval and will decline to perform postmarketing studies if they are not necessary to successfully sell their drugs.<sup>87</sup>

Drug companies spend enormous sums to perform clinical trials, and thus are strongly compelled to present safety and efficacy data in the most favorable light.<sup>88</sup> The academic medical community’s well-documented “publication bias” towards positive findings tends to exacerbate sponsors’ tendencies to selectively disclose favorable results.<sup>89</sup> Clinical researchers often have substantial financial ties to drug manufacturers, which may influence their interpretation of ambiguous data.<sup>90</sup> Some commentators have also expressed concerns that biomedical journals, which receive a

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82. *Id.* at 719.

83. Eisenberg, *supra* note 45, at 347.

84. *Id.* at 347 n.5.

85. Eisenberg, *supra* note 48, at 720.

86. Cahoy, *supra* note 79, at 644–46. Since the performance of expensive clinical trials is generally not considered to fall within the manufacturer’s loss-avoidance duties, “tort incentives that arise from failure to warn cases generally compel information disclosure but not creation.” *Id.* at 640–41. State consumer protection laws act similarly to tort liability and generally only compel the accurate disclosure of “information that companies have generated or plan to generate.” *Id.* at 642–43.

87. *Id.* at 649.

88. Reichman, *supra* note 64, at 4. *See also id.* at 48 (asserting that the results of drug company-funded clinical trials are “increasingly untrustworthy, distorted, or outright fraudulent”).

89. *See, e.g.,* Kay Dickersin & Yuan-I Min, *Publication Bias: The Problem that Won’t Go Away*, 703 ANNALS N.Y. ACAD. SCI. 135 (1993) (observing that a clinical trial is six times or more likely to be published if the results are positive); Scott Ramsey & John Scoggins, *Commentary: Practicing on the Tip of an Information Iceberg? Evidence of Underpublication of Registered Clinical Trials in Oncology*, 13 ONCOLOGIST 925 (2008) (finding that less than one in five registered clinical trials have been published in peer-reviewed journals and attributing this alarming phenomenon to publication bias).

90. Noah, *supra* note 28, at 408–09.

significant amount of revenue from pharmaceutical advertising, are similarly conflicted.<sup>91</sup>

Pharmaceutical firms have been accused of exerting undue influence on medical literature, even to the point of “ghostwriting” journal articles advocating the use of their products to treat particular ailments.<sup>92</sup> They have also been accused of blocking the publication of unfavorable study results.<sup>93</sup> In 2004, in an effort to mitigate the role that medical journals play in disseminating misleading information, the International Committee of Medical Journal Editors (ICMJE), whose members include the Journal of the American Medical Association and the New England Journal of Medicine, met to revise its requirements for manuscripts submission. The revised requirements state that drug companies must register clinical trials on an electronically searchable public database as a precondition for consideration for publication.<sup>94</sup> However, a recent study found that fewer than half of published RCT were adequately registered (i.e., registered before the end of the trial, with the primary endpoint clearly specified).<sup>95</sup> This suggests that informational distortions continue to permeate published clinical trials data.

### *B. Bureaucratic Conservatism within the FDA*

The FDA utilizes its power to control which products enter and remain in the marketplace as the instrumentality for compelling information creation by drug makers.<sup>96</sup> In some cases, political pressures induce the agency to mandate information production that may not yield net social benefits. The FDA’s frequent insistence on the generation of more pre-marketing data than is socially desirable may be attributed to overcompensation for the fact that drug sponsors selectively produce and disclose information so as to maximize profits. In addition, many commentators note

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91. See, e.g., Richard A. Deyo et al., *The Messenger Under Attack – Intimidation of Researchers by Special-Interest Groups*, 336 NEW ENG. J. MED. 1176, 1179 (1997) (suggesting that journals may “need to set up defenses against potential threats of withholding advertising”).

92. See Natasha Singer, *Medical Papers by Ghostwriters Pushed Therapy*, N.Y. TIMES, Aug. 5, 2009, at A1 (“Wyeth contracted with a medical communications company to outline articles, draft them and then solicit top physicians to sign their names, even though many of the doctors contributed little or no writing. . . . [T]he practice went well beyond the case of Wyeth and hormone therapy, involving numerous drugs from other pharmaceutical companies.”).

93. See, e.g., David Blumenthal et al., *Withholding Research Results in Academic Life Sciences: Evidence from a National Survey of Faculty*, 277 JAMA 1224, 1226 (1997) (reporting that some researchers had delayed publication of their studies “to slow dissemination of undesired results”).

94. ICMJE, *Obligation to Register Clinical Trials*, UNIFORM REQUIREMENTS FOR MANUSCRIPTS SUBMITTED TO BIOMEDICAL JOURNALS, [http:// www.icmje.org/ publishing\\_ 10register.html](http://www.icmje.org/publishing_10register.html) (last visited Jan. 13, 2011).

95. Sylvain Mathieu et al., *Comparison of Registered and Published Primary Outcomes in Randomized Controlled Trials*, 302 JAMA 977, 977 (2009).

96. Michael D. Greenberg, *Information, Paternalism, and Rational Decision-Making: The Balance of FDA New Drug Approval*, 13 ALB. L.J. SCI. & TECH. 663, 672 (2003).

that the FDA's assumed role as guarantor of patient welfare has made agency officials inappropriately cautious when guiding the review process.<sup>97</sup>

Agency officials are motivated to avoid Type-I errors (i.e., approving drugs that are not safe and effective), and to disregard Type-II errors (i.e., keeping off the market safe and effective drugs).<sup>98</sup> FDA conservatism stems from the fact that, while the agency is invariably pilloried when an approved drug is later discovered to possess previously unknown harms, the agency rarely faces public rebuke for failing to timely approve promising new therapies.<sup>99</sup> As one government official explained, "every bureaucratic incentive for an individual in the government reviewing a drug' counsels against approval, for '[t]here is no danger of ending up with another Thalidomide if you do not release it.'"<sup>100</sup> Such overcaution has led to ratcheting of premarketing requirements arguably beyond that which maximizes the public good.<sup>101</sup>

Excessive regulation of new drugs risks negating the incentivizing effect of patents, thereby discouraging innovation and negatively impacting public health.<sup>102</sup> Critics have argued that stringent requirements for establishing safety and efficacy prior to market approval actually cause patients more harm than good by denying them access to new medical technologies.<sup>103</sup> Sam Peltzman published influential studies in the early 1970s ex-

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97. Merrill, *supra* note 4, at 1768.

98. HENRY G. GRABOWSKI & JOHN M. VERNON, *THE REGULATION OF PHARMACEUTICALS: BALANCING THE BENEFITS AND RISKS* 10 (1983) (explaining that FDA officials committing Type-I errors may bear heavy personal costs because the effects of such errors are often highly visible and politically charged, whereas the effects of Type-II errors are much less visible and are borne largely by others—patients and drug companies).

99. Elizabeth C. Price, *Teaching the Elephant to Dance: Privatizing the FDA Review Process*, 51 *FOOD & DRUG L.J.* 651, 655 (1996) (noting that "[g]iven the miasma of being damned if they do and ignored if they do not, it is little wonder that the FDA often simply 'does not,' and errs on the side of caution."); Charles Steenburg, *The Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 61 *FOOD & DRUG L.J.* 295, 339–40 (2006).

100. Steenburg, *supra* note 99, at 340 (quoting *Drug Regulation Reform Act of 1978: Hearings Before the Subcomm. on Health and Scientific Research of the S. Comm. on Human Resources*, 95th Cong. 253 (1978) (statement of HEW Secretary Califano)).

101. Between 1977 and 1995, the mean number of pages per new drug application (NDA) increased by 43%, the mean number of patients per NDA increased by 37%, and the mean number of clinical trials per NDA increased by 44%. Reichman, *supra* note 64, at 10. The FDA under the George W. Bush administration made clear its support for the preemption defense, whereby FDA approval would preempt state-law tort claims concerning the approved product. Catherine T. Struve, *Greater and Lesser Powers of Tort Reform: The Primary Jurisdiction Doctrine and State-Law Claims Concerning FDA-Approved Products*, 93 *CORNELL L. REV.* 1039, 1040–42 (2008). Efforts to attenuate tort liability through preemption may exacerbate problems related to the FDA playing the role of guarantor of drug safety and efficacy, promoting the agency's overly conservative approach and compelling it to require more premarketing data than is socially desirable.

102. Katz, *supra* note 7, at 5.

103. See, e.g., Price, *supra* note 99, at 654 ("When the costs of excessive caution are factored in—not only lost profits, jobs, and foregone research and development, but, more importantly, lost lives that could have benefited from products frozen in the FDA queue—the net effect to the American consumer arguably is negative, not positive.") (citing PETER BARTON HUTT & RICHARD A. MERRILL,



aming the impact of the 1962 Amendments on drug development.<sup>104</sup> He observed a sharp post-Amendments decline in the introduction of new drugs (or new chemical entities (NCEs))<sup>105</sup> and concluded that the benefits of saving consumers from ineffective drugs were outweighed by the negative effects on innovation.<sup>106</sup> Peltzman's critique was followed by a series of articles by William Wardell, Louis Lasagna, and other prominent academic scientists who contended that excessive U.S. regulation had created a substantial drug "lag" in comparison to other industrialized countries.<sup>107</sup> While some commentators criticized Peltzman's analysis, and drug development rebounded during the 1980s and 1990s, the general consensus is that the 1962 Amendments created a significant regulatory obstacle to the introduction of new drugs.<sup>108</sup>

FDA requirements have at times led to frustration on the part of patients and physicians seeking access to drugs despite information gaps about safety and efficacy. In 1979, the Supreme Court ruled against terminally ill cancer patients seeking access to an unapproved drug, laetrile, overturning the Tenth Circuit's ruling that the FDCA was inapplicable to terminally ill patients whose need for safety and efficacy in treatment could not be measured.<sup>109</sup> Without a constitutional right, patients were left with an informal, ad hoc process for "compassionate" use of an investigational new drug (IND), which allowed patients to request FDA permission to use unapproved drugs on a case-by-case basis.<sup>110</sup>

The FDA implemented a formal process for patients to access unapproved new drugs outside a clinical trial in 1987 in response to mounting

FOOD & DRUG LAW: CASES & MATERIALS 534 (2d ed. 1991)).

104. SAM PELTZMAN, REGULATION OF PHARMACEUTICAL INNOVATION: THE 1962 AMENDMENTS (1974) [hereinafter PELTZMAN, PHARMACEUTICAL INNOVATION]; Sam Peltzman, "An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments:" A Reply, 81 J. POL. ECON'Y. 1049 (1973) [hereinafter Peltzman, *Consumer Protection Legislation*].

105. Peltzman, *Consumer Protection Legislation*, *supra* note 104, at 1052-58.

106. PELTZMAN, PHARMACEUTICAL INNOVATION, *supra* note 104, at 51-73; Peltzman, *Consumer Protection Legislation*, *supra* note 1, at 1059.

107. See, e.g., WILLIAM M. WARDELL & LOUIS LASAGNA, REGULATION AND DRUG DEVELOPMENT (1975); William M. Wardell, *A Close Inspection of the "Calm Look": Rhetorical Amblyopia and Selective Amnesia at the Food and Drug Administration*, 239 JAMA 2004, 2007-09 (1978). See generally Leonard G. Schiffrin, *Lessons from the Drug Lag: A Retrospective Analysis of the 1962 Drug Regulations*, 5 HARV. J.L. & PUB. POL'Y 91 (1982) (summarizing articles and studies on the existence and extent of the drug lag in the United States).

108. Katz, *supra* note 7, at 9.

109. *United States v. Rutherford*, 442 U.S. 544, 556-59 (1979).

110. Judy Vale, Note, *Expanding Expanded Access: How the Food and Drug Administration Can Achieve Better Access to Experimental Drugs for Seriously Ill Patients*, 96 GEO. L.J. 2143, 2149-50, 2150 n.53 (2008). See also Lois K. Perrin, Note, *The Catch-22 for Persons with AIDS: To Have or Not to Have Easy Access to Experimental Therapies and Early Approval for New Drugs*, 69 S. CAL. L. REV. 105, 119 (1995) (noting that compassionate-use INDs were granted by the FDA when the "manufacturer [was] willing to supply the drug, a physician [was] willing to prescribe it, a patient [was] willing to give informed consent, and [there was] some basis for believing that the treatment [was] not an outright fraud or poison.") (quoting INSTITUTE OF MEDICINE, CONFERENCE SUMMARY, EXPANDING ACCESS TO INVESTIGATIONAL THERAPIES FOR HIV INFECTION AND AIDS 7, 8-9 (1991)).

pressure from AIDS activists.<sup>111</sup> The agency permitted “treatment use of an investigational drug” (treatment IND) so long as four criteria were met: (1) the drug was intended to treat a “serious or immediately life-threatening disease”; (2) there was “no comparable or satisfactory alternative drug” or treatment for that patient population and disease stage; (3) the drug was “under investigation in a controlled clinical trial” or all trials were completed; and (4) the drug sponsor was “actively pursuing marketing approval” of the drug with “due diligence.”<sup>112</sup> Sponsors could charge patients for treatment IND use if there was “adequate enrollment” in ongoing clinical trials, the charge did “not constitute commercial marketing” of an unapproved drug, the drug was not “commercially promoted or advertised,” and the sponsor was “actively pursuing marketing approval with due diligence.”<sup>113</sup>

The category of alternative therapies that would bar access to a treatment IND under the second criterion listed above may include off-label uses of approved drugs if such use is supported by compelling literature evidence.<sup>114</sup> This regulatory stance is arguably nonsensical in that it allows for the unknown risks of off-label use, perhaps before other approved therapies are tried, but not for the unknown risks of a treatment IND.<sup>115</sup> The distinction may not be tenable, as off-label uses of approved drugs and uses of unapproved drugs are often comparably supported by the medical literature.<sup>116</sup>

The FDAMA of 1997 granted the FDA explicit authority to allow expanded access to unapproved drugs. Congress distinguished a “treatment IND” in which many individuals sought access to the experimental drug from “individual patient access” in which the drug was offered to a specific patient.<sup>117</sup> However, the FDA did not propose new regulations until 2006, shortly after the Abigail Alliance, an advocacy group named after a woman who succumbed to cancer after having been denied enrollment in a clinical trial, earned a short-lived victory in the D.C. Circuit Court of Appeals. The court initially ruled in favor of a constitutional right for ter-

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111. Vale, *supra* note 110, at 2150.

112. Investigational New Drug Application, 21 C.F.R. § 312.34 (2007). This section was removed on August 13, 2009, effective October 13, 2009, and replaced in substance by 21 C.F.R. §§ 312.305–.320. *See* Expanded Access to Investigational Drugs for Treatment Uses, 74 Fed. Reg. 40,900, 40,942 (Aug. 13, 2009) (to be codified at 21 C.F.R. pt. 312, 316).

113. 21 C.F.R. § 312.7(d)(2) (2007). This paragraph was removed on August 13, 2009, effective October 13, 2009, and replaced in substance by § 312.8. *See* Charging for Investigational Drugs Under an Investigational New Drug Application, 74 Fed. Reg. 40,872, 40,899 (Aug. 13, 2009) (to be codified at 21 C.F.R. pt. 312).

114. Vale, *supra* note 110, at 2162. *See also* FOOD AND DRUG ADMIN., U.S. DEP’T OF HEALTH AND HUMAN SERVS., GUIDANCE FOR INDUSTRY: AVAILABLE THERAPY, July 2004, available at [http://www.fda.gov/Regulatory Information/Guidances/ucm126586.htm](http://www.fda.gov/Regulatory%20Information/Guidances/ucm126586.htm).

115. Vale, *supra* note 110, at 2162–63.

116. *Id.*

117. *Id.* at 2154–55.

minally ill patients to access experimental drugs without FDA interference but reversed after hearing the case *en banc*.<sup>118</sup>

The new regulations created three tiers of expanded access with varying levels of safety and efficacy requirements.<sup>119</sup> In keeping with past policy, expanded access programs must “not interfere with the initiation, conduct, or completion of clinical investigations” required for market approval.<sup>120</sup> In order to be eligible for expanded access, the FDA must determine that the patient cannot obtain the drug through a clinical trial.<sup>121</sup> Serious illnesses may be treated with Phase III and sometimes Phase II drugs, while treatments for immediately life-threatening conditions may be at any phase.<sup>122</sup> The FDA regulations allow manufacturers to charge patients seeking drugs under expanded access programs so long as doing so will “not interfere with developing the drug for marketing approval.”<sup>123</sup>

The new expanded access regulations differ from previous versions in that they explicitly protect the viability of clinical trials. Drug companies may have been reluctant to offer expanded access under the 1987 regulations for fear of losing potential subjects, who would likely opt for expanded access over enrollment in clinical trials so as to avoid the possibility of receiving placebos or other less desired treatments.<sup>124</sup> The new rules eliminate this problem by requiring individual patients seeking expanded access to show that they cannot obtain the drug through a clinical trial.<sup>125</sup> Similar protection for clinical trials is provided in the other two tiers of expanded access, as it must be shown that any expanded access program will “not interfere with the initiation, conduct, or completion of clinical investigations” supporting marketing approval.<sup>126</sup>

In 2009, the FDA finalized its new regulations governing expanded access.<sup>127</sup> Under these regulations, the FDA must approve patient participation in an expanded access program. Drug companies must seek FDA permission to charge for therapies and are prohibited from profiting from expanded access.<sup>128</sup> In rare circumstances, the new rules allow a firm to

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118. *Abigail Alliance for Better Access to Dev. Drugs v. Eschenbach*, 445 F.3d 470 (D.C. Cir. 2006) *rev'd en banc*, 495 F.3d 695 (D.C. Cir. 2007).

119. *Vale*, *supra* note 110, at 2145. *See also* Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. 75,147, 75,150, 75,157 (Dec. 14, 2006) (to be codified at 21 C.F.R. pt. 312).

120. Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. at 75,151.

121. *Id.* at 75,153.

122. *Id.* at 75,155.

123. *See* Charging for Investigational Drugs, 71 Fed. Reg. 75,168, 75,172 (Dec. 14, 2006) (to be codified at 21 C.F.R. pt. 312).

124. *Vale*, *supra* note 110, at 2159–60.

125. *Id.* *See* Expanded Access to Investigational New Drugs for Treatment Use, 71 Fed. Reg. at 75,152.

126. Expanded Access to Investigational New Drugs for Treatment Use, 71 Fed. Reg. at 75,151.

127. *See* Jennifer Corbett Dooren, *FDA Sets New Rules on Experimental Drugs*, WALL ST. J., Aug. 13, 2009, at D3.

128. *See id.*

charge for a clinical trial, but only when the drug sponsor can show that the drug cannot be developed without charging patients.<sup>129</sup>

### *C. Lack of Transparency in the Drug Review Process*

The opacity of the regulatory review process reduces the social utility of the information that is generated. The requirements for FDA approval promote the production of information about a drug's effects, but confidentiality policies minimize disclosure.<sup>130</sup> Information about the safety and efficacy of new drugs arguably has greater value to the drug sponsor than its scientific merit alone would warrant because it is a prerequisite to market entry.<sup>131</sup> This value premium created by the existing regulatory regime may heighten drug companies' desire for confidentiality and trade secret protection.

Under existing FDA regulations, applicants do not have to publicly disclose that an NDA has been filed, nor need they inform the public that an application has been withdrawn.<sup>132</sup> Although applicants must file periodic reports summarizing information about premarketing studies, the existence of such studies may remain undisclosed until the NDA is approved.<sup>133</sup> Such restrictions allow companies to exert a great deal of control over information related to their products prior to marketing approval. Even after approval, detailed data about the drug's effects are routinely concealed.<sup>134</sup>

The Freedom of Information Act (FOIA), enacted in 1966 as an amendment to the Administrative Procedure Act, is designed to increase

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129. See *id.* See also Charging for Investigational Drugs Under an Investigational New Drug Application, 74 Fed. Reg. 40,872, 40,873 (Aug. 13, 2009) (to be codified at 21 C.F.R. pt. 312).

130. Cahoy, *supra* note 79, at 631. See also Merrill, *supra* note 4, at 1785 (noting that, since the drug approval system was established in 1938, the FDA has taken the position that the data it receives from drug sponsors is confidential information that may not be disclosed without permission of the owner).

131. Eisenberg, *supra* note 45, at 381. See also James T. O'Reilly, *Knowledge is Power: Legislative Control of Drug Industry Trade Secrets*, 54 U. CIN. L. REV. 1, 4 (1985).

132. See 21 C.F.R. § 312.130(a) (2009) ("The existence of an investigational new drug application will not be disclosed by FDA unless it has previously been publicly disclosed or acknowledged.").

133. See 21 C.F.R. § 314.430(b) (2009) ("FDA will not publicly disclose the existence of an application or abbreviated application before an approval letter is sent to the applicant . . ."). Once the FDA review panel completes its evaluation of an NDA, it sends the submitter an action letter. This action letter takes one of three forms: approved, not approvable, and approvable. An approved letter notifies the sponsor that the drug may enter the market and outlines the labeling and other postmarketing requirements. Not approvable letters are fairly unusual, as problems in an NDA are typically set forth in an approvable letter. An approvable letter informs the applicant that specific actions must be taken before the drug can be approved. The required action may be trivial, or it may involve the performance of additional clinical trials. See Liora Sukhatme, Note, *Deterring Fraud: Mandatory Disclosure and the FDA Drug Approval Process*, 82 N.Y.U. L. REV. 1210, 1220–21 (2007). For an overview of the FDA approval process, see *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, FOOD AND DRUG ADMIN., <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm> (last updated Feb. 22, 2010).

134. Cahoy, *supra* note 79, at 631–32.

the transparency of the federal agencies.<sup>135</sup> FOIA requires agencies to make “records promptly available to any person” upon request.<sup>136</sup> However, agencies are exempt from the disclosure requirements of the FOIA if the information requested falls within one of nine express exemptions.<sup>137</sup> Exemption 4 includes “trade secrets and commercial or financial information obtained from a person and privileged or confidential”.<sup>138</sup> In *Public Citizen Health Research Group v. FDA*, a federal appeals court held that the safety and efficacy information required for FDA approval fell under the FOIA exemption for confidential commercial information.<sup>139</sup>

The Hatch–Waxman Act of 1984 created a system whereby generic manufacturers may rely on pioneering firms’ raw data to support their ANDA,<sup>140</sup> but generic firms generally do not have access to such data.<sup>141</sup> Although the FOIA requires that the FDA disclose the information contained in an approved application upon request absent “extraordinary circumstances,” FDA regulations make it quite easy to establish extraordinary circumstances.<sup>142</sup> When the FDA receives an FOIA request from a generic firm seeking more information about its drug, it notifies the NDA sponsor of the request. If the pioneering firm can make a convincing argument that the raw data provides the manufacturer with a continuing commercial advantage (e.g., the data is necessary to support an application for marketing in a foreign country), the firm has demonstrated the “extraordinary circumstances” to qualify for an exemption from the FOIA and the generic firm is denied access to the data.<sup>143</sup> Thus, a generic firm’s

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135. See Freedom of Information Act of 1966, Pub. L. No. 89-487, 80 Stat. 250 (codified as amended at 5 U.S.C. § 552 (2006)).

136. *Id.* § 552(a)(3)(A).

137. *Id.* § 552(b).

138. *Id.* § 552(b)(4). Proponents of trade secrecy have relied on 21 U.S.C. § 301(j) of the FDACA, which prohibits the disclosure of “any information acquired under the authority of section [505] . . . concerning any method or process which as a trade secret is entitled to protection . . . .” Eisenberg, *supra* note 45, at 380 n.129. Section 331(j) of the FDCA prohibits the disclosure of “any method or process which as a trade secret is entitled to protection.” The FDA has consistently treated this provision as addressing essentially the same material covered by Exemption 4 of the FOIA. See Evan Diamond, *Reverse-FOIA Limitations on Agency Actions to Disclose Human Gene Therapy Clinical Trial Data*, 63 FOOD & DRUG L. J. 321, 356 (2008). FDA’s general regulation implementing section 301(j) of the FDCA can be found at 21 C.F.R. § 20.61. 21 C.F.R. § 20.61(c) provides that data or information submitted to FDA that is trade secret or commercial confidential information is not available for public disclosure.

139. 704 F.2d 1280, 1290–91 (D.C. Cir. 1983).

140. See *supra* Part II.C.

141. O’Reilly, *supra* note 131, at 21.

142. Cahoy, *supra* note 79, at 631–32.

143. O’Reilly, *supra* note 131, at 22–23. The Hatch–Waxman Act does not raise any “taking” issues under the constitution because of the term of years during which drug sponsors are guaranteed protection of their data. *Id.* at 25. However, these issues may come into play if future legislative initiatives alter pioneering firms’ expectations regarding the confidentiality of data submitted to the FDA. *Id.* See also Ruckelshaus v. Monsanto Co., 467 U.S. 986 (1984) (discussing, in a different context, constitutional taking issues involved in a government scheme of promoting second firm uses of pioneer’s testing data).

knowledge of its products primarily comes from published patent data about the compound, the data summary issued by the FDA at the time of the pioneer drug's approval, any published scientific literature about the drug, and the bioequivalence testing data that generic firms must generate in order to gain approval of its ANDA.<sup>144</sup>

Although the underlying data remain largely undisclosed, the FDA disseminates information about approved drugs in the form of the "required labeling that must accompany the product[s] in the market."<sup>145</sup> In addition, in recent years the FDA has begun putting select information about approved drugs on its website.<sup>146</sup> The FDA website includes information about the drug's approval history, correspondence, and supporting analyses by agency staff.<sup>147</sup> Nonetheless, the drug approval process remains largely nontransparent, and the content of negotiations between the FDA and the drug sponsor "remains hidden behind the curtain, shrouded in confidentiality rationales."<sup>148</sup>

This veil of secrecy greatly reduces the social value of the information generated by the FDA approval process. Keeping the data derived from clinical trials confidential impedes innovation and deprives patients and doctors of information with which to make treatment decisions.<sup>149</sup> The social loss from secrecy compounds as advances in information technology create opportunities for data aggregation and mining to decipher trends regarding the effects of new drugs.<sup>150</sup> While the information contained in the product label may be all that most end users want,<sup>151</sup> it is undesirable for the FDA to hoard raw clinical trials' data in this manner. This regulatory practice belies the fact that scientific experts may, and often do, disagree about the conclusions to be drawn from a given study. Obscuring this fact does a disservice to patients, doctors, and the general public.

Lack of transparency in the drug review process "exposes drug companies and regulators to charges of bad faith and incompetence, compromising the signaling function of regulatory approval as a marker of safety and efficacy."<sup>152</sup> Secrecy inevitably leads to public suspicion, especially when previously unknown product risks surface postapproval.<sup>153</sup> Consumers, doctors, and scientists recently implored the FDA to disclose more

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144. O'Reilly, *supra* note 131, at 22.

145. Eisenberg, *supra* note 45, at 382.

146. *See, e.g.*, U.S. DEP'T HEALTH & HUMAN SERVS., FDA, <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails> (last visited Jan. 13, 2011)

147. Eisenberg, *supra* note 45, at 382.

148. James T. O'Reilly, *Drug Review "Behind the Curtain": A Response to Professor Struve*, 93 CORNELL L. REV. 1075, 1075 (2008).

149. Eisenberg, *supra* note 45, at 383.

150. *Id.*

151. *Id.*

152. Eisenberg, *supra* note 48, at 720.

153. *Id.* at 739.

information about the results of clinical trials as well as negotiations between drug sponsors and the agency undertaken during the course of pre-marketing review.<sup>154</sup> Some proposed allowing FDA scientists to publicly disclose their opinions about a drug when the scientists disagree with a final agency approval decision.<sup>155</sup> Deputy Commissioner Joshua Sharfstein was cool to this proposal, noting that reviewing scientists often “‘disagree sharply,’ and airing those differences might erode the public’s trust in FDA decisions.”<sup>156</sup>

#### *D. Inherent Limitations of RCT*

Even if drug sponsors and the FDA were compelled to generate and disclose the socially optimal supply of clinical-trial data, significant information gaps would remain under the existing regulatory system. “As FDA Commissioner George P. Larrick explained to a House subcommittee in 1964, ‘even the most extensive’ clinical investigation will reveal only a fraction of the information” about the effects of a drug in the treatment setting.<sup>157</sup> The typical clinical trial involves a narrow population of subjects who are carefully screened and selected, and who are closely monitored under special protocols. It is highly unlikely that the results of such trials can completely predict the drug’s effects in the broader population under real world conditions

where patients do not always take their medicines on time or at all; where patients might have other medical problems or be of advanced age or in frail health; and where they have comorbidities or unusual diets, or they fill prescriptions for medications or dietary supplements that interact with one another, subtly or otherwise.<sup>158</sup>

Compounding problems related to significant differences between the use of a drug in a controlled environment and in the real world, it is statistically highly unlikely to detect relatively infrequent effects during the course of a clinical trial.<sup>159</sup> Because Phase III trials typically enroll 3,000

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154. Jared A. Favole, *FDA Pressed for Transparency*, WALL ST. J., June 24, 2009, <http://online.wsj.com/article/SB124588492308150255.html>

155. *Id.*

156. *Id.*

157. Steenburg, *supra* note 99, at 297 (citing *Drug Safety (Part One): Hearings Before a Subcomm. of the H. Comm. on Government Operations*, 88th Cong. 152 (1964) [hereinafter *1964 Hearings*], reprinted in FDA, LEGISLATIVE HISTORY OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT AND ITS AMENDMENTS, App. D at 152 (1979)).

158. Scott Gottlieb, *Opening Pandora’s Pillbox: Using Modern Information Tools to Improve Drug Safety: The FDA Could Improve its Safety Monitoring Program Without Burdening its Drug Approval Process*, 24 HEALTH AFF. 938, 939 (2005).

159. Steenburg, *supra* note 99, at 297. See also Anita Bernstein & Joseph Bernstein, *An Informa-*

to 4,000 patients, such studies “will only detect adverse [drug] reactions that occur at a rate of 1-in-1000 or higher.”<sup>160</sup> Louis Lasagna noted in 1983 that a study would require “more than 600,000 participants in order to have a ninety-five percent chance of detecting an adverse reaction that plagues one or two patients out of every 10,000 treated.”<sup>161</sup> Such a relatively uncommon reaction could nonetheless impact hundreds of patients once the drug reached the market. Moreover, even common effects will not be detected in a clinical trial if they only emerge after long-term use of the drug.<sup>162</sup>

Previously, “the FDA generally preferred the submission of data from a homogeneous population of subject” so as to minimize problems of data interpretation related to confounding variables.<sup>163</sup> Now, however, the agency is statutorily obligated to develop guidelines to ensure participation in clinical trials by women and minorities.<sup>164</sup> This leads to the generation of data that is more relevant to the real world treatment setting, but also noisier and more difficult to interpret.<sup>165</sup> Investigators and the agency have sought to address this problem with innovative trial designs such as adaptive clinical trials, but these solutions are imperfect and could potentially increase development costs.<sup>166</sup>

Despite extensive FDA review, “[i]t is simply not possible to identify all the side effects of drugs before they are marketed. The difficulty is not a failure of the . . . drug-approval process; it is the expected consequence

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*tion Prescription for Drug Regulation*, 54 BUFF. L. REV. 569, 580–81 (2006) (noting that a study may enroll too few subjects to achieve the “statistical power to discern differences in the rates of common adverse effects,” and that “the truth might emerge only from large-number, postmarketing data”).

160. Noah, *supra* note 18, at 459.

161. Steenburg, *supra* note 99 at 297 (citing Louis Lasagna, *Discovering Adverse Drug Reactions*, 249 JAMA 2224, 2225 (1983)).

162. *Id.* See also Struve, *supra* note 32, at 598–99 (observing that, even if rigorously conducted, “[c]linical trials normally will fail to reveal a number of types of problems: those that occur relatively rarely, those involving relatively subtle increases in the risk of already common problems, those that disproportionately affect a population subset not represented in the trial, and those with a long latency period”); Gottlieb, *supra* note 158, at 939–940 (noting that longer trials will not make drugs safer “because the data that these trials generate will never reach a magnitude sufficient to unearth the kinds of side effects that” became apparent in high-profile cases such as those involving the painkiller Vioxx or the class of antidepressives known as selective serotonin reuptake inhibitors (SSRIs)).

163. Eisenberg, *supra* note 45, at 375.

164. See *id.*; 21 U.S.C. § 355(b)(1) (2006).

165. Eisenberg, *supra* note 45, at 375.

166. U.S. DEP’T HEALTH AND HUMAN SERVS., REALIZING THE POTENTIAL OF PHARMACOGENOMICS: OPPORTUNITIES AND CHALLENGES 22–23 (May 2008), available at [http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS\\_PGX\\_report.pdf](http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_PGX_report.pdf) (explaining that, in contrast to conventional “clinical trials in which subject selection and related study design aspects are determined in advance . . . [a]daptive clinical trial designs aim to be iterative and flexible.” However, adaptive designs have many pitfalls and “often are not used in Phase III trials because interim results are not confirmative and can be misleading.”). See also Bridget M. Kuehn, *Industry, FDA Warm to “Adaptive” Trials*, 296 JAMA 1955 (2006); Scott Gottlieb, M.D., Deputy Comm’r for Med. and Scientific Affairs, Food and Drug Admin., Speech before 2006 Conference on Adaptive Trial Design (July 10, 2006), available at <http://www.fda.gov/NewsEvents/Speeches/ucm051901.htm>.



of the biologic diversity of humans.”<sup>167</sup> Indeed, as Commissioner Larrick observed back in 1964, “the early period following general marketing of a drug may be regarded as a final step in the testing of the product.”<sup>168</sup> The FDA tacitly acknowledged the information gaps that remain at the time of drug approval in 2000 when it proposed the addition of a special symbol to the label of drugs for their first three years on the market.<sup>169</sup>

While much of the commentary regarding the limitations of RCT focuses on the risks of failing to detect safety problems, such limitations also come into play when considering the efficacy determination. For example, drugs which are efficacious in a subgroup of patients enrolled in a clinical trial may fail to demonstrate statistical significance of efficacy as required by the FDA. Allowing trends to emerge from treatment of a broader patient population than that enrolled in an RCT may lead to better treatment options for individual patients.

Patient under-enrollment in clinical trials presents a significant logistical barrier to the accumulation of information about drug safety and efficacy. A recent study found that more than one trial in five sponsored by the National Cancer Institute failed to enroll a single patient, and only half reached the minimum needed for a meaningful result.<sup>170</sup> Doctors often have strong financial disincentives to participate in clinical trials.<sup>171</sup> Moreover, patients are often reluctant to become subjects in formal studies. Many fear receiving “treatment determined by the flip of a coin” and others find the idea of enrolling in a clinical trial “overwhelming when they are trying to save their lives.”<sup>172</sup> Perversely, the patients who are most

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167. Alastair J.J. Wood et al., *Making Medicines Safer — The Need for an Independent Drug Safety Board*, 339 NEW ENG. J. MED. 1851, 1852 (1998). See also JERRY AVORN, POWERFUL MEDICINES: THE BENEFITS, RISKS, AND COSTS OF PRESCRIPTION DRUGS 72 (2005) (stating that even with FDA approval, “[w]hen a new drug is first marketed, little is proven about its safety and effectiveness compared to existing alternatives, and the situation is often no clearer years or decades later.”)

168. Steenburg, *supra* note 99, at 298 (citing *1964 Hearings, supra* note 157, at 152).

169. See Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels, 65 Fed. Reg. 81,082, 81,088 (proposed Dec. 22, 2000) (to be codified at 21 C.F.R. § 201.57(a)(2)) (proposing to require the placement of an inverted solid black triangle on the labels of drugs approved for fewer than three years and that contain a new molecular entity, a new active ingredient combination, are indicated for a new population, or utilize a different delivery system).

170. Gregory A. Curt & Bruce A. Chabner, Editorial, *One in Five Cancer Clinical Trials is Published: A Terrible Symptom—What’s the Diagnosis?*, 13 ONCOLOGIST 923, 923 (2008). See also Gina Kolata, *Lack of Study Volunteers is Said to Hobble Fight Against Cancer*, N.Y. TIMES, Aug. 3, 2009, at A1 (noting that only about three percent of adult cancer patients participate in clinical trials).

171. Kolata, *supra* note 170 (explaining that oncologists typically receive 60 percent to 80 percent of their revenue from administration of chemotherapy. The doctors buy the medication and are reimbursed by insurance companies for slightly more than the drugs’ cost. But if patients are enrolled in clinical trials, the drugs are typically paid for by the drug sponsor, and the physician receives nothing. Moreover, doctors are typically poorly reimbursed for the time required to submit paperwork and obtain informed consent from patients.)

172. *Id.* at A14.

eager to participate in trials are often those with few or no options for whom the investigational drug offers the last hope for a meaningful therapeutic benefit.<sup>173</sup>

### *E. Unexplored Experiential Data*

The existing regulatory regime fails to capture a vast amount of potentially useful experiential information about newly approved medical products. Case reports and formal observational studies collect some information about treatment outcomes, but this represents only a small fraction of patient encounters with new drugs. Commentators have argued that the FDA should place greater emphasis on alternatives to RCT.<sup>174</sup> Alternative approaches to traditional, controlled scientific experimentation can produce valuable information about the effects of drugs while maintaining respect for patient autonomy.<sup>175</sup>

Practical trials, where patients are not randomized and participants are not blinded, lack the statistical precision of RCT. “[T]hese [types] of trials can nonetheless be rigorous if sample sizes are large and the [means] for evaluating [the data] are well defined.”<sup>176</sup> “Statistical tools for conducting rigorous analyses . . . of practical data . . . and methods for aggregating very large [data sets] have [significantly] advanced since [the advent of RCT as the centerpiece] of the drug approval process.”<sup>177</sup>

Previously unknown benefits of marketed drugs are often discovered serendipitously by clinicians in the treatment setting.<sup>178</sup> Anecdotal experience may cumulate, and in the process evolve into a valuable source of information.<sup>179</sup> Although anecdotal information may not be suitable for statistical analysis, it can be a useful springboard for generating scientific hypothesis and establishing research priority strategies.<sup>180</sup> “Outcomes research” seeks to assess the effectiveness of particular therapeutic interventions under real world conditions by assembling clinical data from large numbers of comparable patients.<sup>181</sup> “Such an approach allows the experiences of many physicians to be pooled, so that the individual physician does not have to rely exclusively on his own experience.”<sup>182</sup> For instance,

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173. *Id.*

174. *See, e.g.*, Gottlieb, *supra* note 158.

175. Steven R. Salbu, *Regulation of Drug Treatments for HIV and AIDS: A Contractarian Model of Access*, 11 *YALE J. ON REG.* 401, 435 (1994).

176. Gottlieb, *supra* note 158, at 947.

177. *Id.*

178. Noah, *supra* note 18, at 460.

179. *See* Lincoln E. Moses, *The Series of Consecutive Cases as a Device for Assessing Outcomes of Intervention*, 311 *NEW ENG. J. MED.* 705, 709–10 (1984).

180. Salbu, *supra* note 175, at 432.

181. *See* Christopher Anderson, *Measuring What Works in Health Care*, 263 *SCIENCE* 1080, 1080 (1994).

182. Noah, *supra* note 28, at 385 (quoting Alain C. Enthoven, *Shattuck Lecture—Cutting Cost*

longitudinal observational studies permit reasonable inferences to be drawn by comparing outcomes in individual patients undergoing different courses of treatment.<sup>183</sup> Some commentators have argued that outcomes research may provide more meaningful guidance than RCT about a drug's effectiveness in the real world treatment setting.<sup>184</sup>

Yet the FDA has shown reluctance to consider information produced outside the strict parameters of the RCT. For instance, the data generated from treatment via expanded access programs could be used to fill the informational void created when drugs are approved through the fast-track programs, as many drugs that are eligible for expanded access are also eligible for fast-track approval.<sup>185</sup> Yet the FDA generally disregards the data generated from expanded access programs because they derive from use in the treatment setting under real world conditions, as opposed to the controlled environment of a formal trial.<sup>186</sup>

Notably, the agency has defended criticism of its stalled fast-track programs by pointing out that patients may receive access to unapproved drugs through expanded access programs.<sup>187</sup> Thus, we are left with a bizarrely contorted regulatory regime in which the FDA, in the name of patient welfare, demands expensive, time-consuming experimentation before approving a drug for market. Patients eligible for RCT are forced to participate in a trial if they are to have a chance of receiving the new drug. Those who are not eligible for RCT may obtain access to the drug in the treatment setting, but information gleaned from use of the drug in this context is largely ignored by the agency.

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*Without Cutting the Quality of Care*, 298 NEW ENG. J. MED. 1229, 1236 (1978)).

183. Sheldon Greenfield, *The State of Outcome Research: Are We on Target?*, 320 NEW ENG. J. MED. 1142 (1989).

184. See John Concato et al., *Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs*, 342 NEW ENG. J. MED. 1887, 1890-92 (2000); Alvan R. Feinstein & Ralph I. Horowitz, *Problems in the "Evidence" of "Evidence-Based Medicine"*, 103 AM. J. MED. 529 (1997); J. Andre Knottnerus & Geert Jan Dinant, Editorial, *Medicine-Based Evidence, a Prerequisite for Evidence-Based Medicine*, 315 BRIT. MED. J. 1109 (1997); see also Nick Black, *Why We Need Observational Studies to Evaluate the Effectiveness of Health Care*, 312 BRIT. MED. J. 1215 (1996) (arguing that these research methods can complement one another).

185. Vale, *supra* note 110, at 2171.

186. *Id.* at 2172. The FDA is disinclined to give weight to data derived from expanded access programs out of fears that falsely positive data could unduly raise patients' expectations while negative data could unfairly gauge the utility of the experimental drug. *Id.* at 2173. Because of the alternative treatment rule, the patients who receive drugs through expanded access programs are often extremely ill and may not benefit even from an effective drug. *Id.*

187. Szabo, *supra* note 77.

## IV. RECENT INITIATIVES TO RESOLVE THE INFORMATION PROBLEM

A. *Clinical Trials*

A variety of proposals have been advanced to address recognized deficiencies in the current drug regulatory system. Some observers argue for private third-party review of new medical products.<sup>188</sup> These advocates focus on the problem of bureaucratic conservatism and the downside of excessive premarketing data requirements. Draft bills circulated in 1995 contemplated statutory changes to permit drug manufacturers “to contract with qualified private entities to review their [NDAs]” and submit recommendations to the FDA regarding the safety and efficacy of their products.<sup>189</sup>

On the other end of the ideological spectrum are those who champion government funding and government oversight of clinical trials.<sup>190</sup> Rather than compelling private firms to pay for costly clinical trials and allowing them to retain the data as confidential, these commentators favor using public funds to generate information about the effects of drugs.<sup>191</sup> Proposals for treating clinical trials data as a public good emphasize private firms’ motivations to selectively produce and disclose information about their products.<sup>192</sup>

Other efforts seek to increase the amount of publicly available clinical trials data while preserving the traditional roles of the FDA and drug sponsors. In 2004, GlaxoSmithKline published findings demonstrating that its drug Paxil was effective for the treatment of adolescent depression but declined to publish the results of a different study raising concerns about children experiencing suicidal thoughts while on Paxil.<sup>193</sup> This prompted

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188. See, e.g., Price, *supra* note 99, at 651–66 (arguing for privatization of the review process, but nonetheless insisting that “[p]roducts would be judged by the same stringent safety and efficacy standards used today, ensuring the consumer that, no matter what entity conducts the review (public or private), the American ‘gold standard’ of safety and efficacy would remain uncompromised”).

189. Merrill, *supra* note 4, at 1857. Another proposal would have required the FDA to accept or reject the approval decisions of regulatory authorities of the European Community or the United Kingdom. *Id.* at 1862. The agency would have been “required to justify its failure” to approve any drug which “had satisfied the approval standards of . . . designated [foreign] regulatory bodies. *Id.*”

190. Reichman, *supra* note 64, at 51–64. See also Tracy R. Lewis et al., *The Case for Public Funding and Public Oversight of Clinical Trials*, THE ECONOMISTS’ VOICE, Jan. 2007, available at <http://www.bepress.com/ev/vol4/iss1/art3>; Dean Baker, *The Benefits and Savings from Publicly-Funded Clinical Trials of Prescription Drugs*, CENTER FOR ECONOMIC AND POLICY RESEARCH, Mar. 2008, available at [http://www.cepr.net/documents/publications/clinicaltrials\\_2008\\_03.pdf](http://www.cepr.net/documents/publications/clinicaltrials_2008_03.pdf).

191. Reichman, *supra* note 64, at 51.

192. See *Id.* at 50 (arguing that even if drug companies are obligated to disclose safety and efficacy data, they will still be motivated to avoid studies that could produce unfavorable results). For example, the data could suggest that the drug be used for a narrower set of indications, be limited to a smaller subgroup patient population, or that its use be discontinued entirely. *Id.*

193. Snigdha Prakash, *Morning Edition: Drug Trial Results Disclosure*, NATIONAL PUBLIC RADIO (June 11, 2004), <http://www.npr.org/templates/rundowns/rundown.php?prgId=3&prgDate=6-11-2004>. See also *Update on SSRI/Suicide Controversy: GSK Releases Clinical Trial Data on Paxil*

commentators to call for a new federal law that would compel manufacturers to register all significant clinical trials into a public database that would also publish results when the studies ended.<sup>194</sup> Title VIII of the Food and Drug Administration Amendments of 2007 (FDAAA) directed that additional information be made publicly available through a clinical trial registry established by the National Institutes of Health (NIH) /National Library of Medicine (NLM) in 1997.<sup>195</sup>

In a significant break from past practice, the existence and details of clinical trials are now widely disseminated on the website “Clinical-Trials.gov.”<sup>196</sup> The 2007 Amendments effectively override customary confidentiality by requiring that any “controlled clinical investigation,” other than a Phase I trial, that is part of an NDA be registered on the database.<sup>197</sup> The registry databank must include summary documents and links to FDA assessments of the results of clinical trials.<sup>198</sup>

Other proposals seek to increase incentives for drug manufacturers to voluntarily produce and disclose clinical trials data. These include suggestions that drug companies be required to reveal results of clinical trials in exchange for grants of data exclusivity.<sup>199</sup> Such arguments seek to equate public access to the data underlying FDA approval with the quid pro quo of the patent system, in which exclusivity is granted in exchange for information disclosure.<sup>200</sup> A related proposal would require drug manufacturers to register trials at the outset if they wish to one day use the data as part of an NDA.<sup>201</sup> Other commentators focus on ameliorating undesirable effects of tort liability, which may dissuade drug companies from voluntarily performing clinical trials.<sup>202</sup>

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*Use In Children*, BROWN UNIV. PSYCHOPHARMACOLOGY UPDATE, Aug. 2004, at 2.

194. Editorial, *For Honest Reports of Drug Trials*, N.Y. TIMES, Sept. 11, 2004, at A14. See also Press Release, American Medical Association, AMA Recommends that DHHS Establish a Registry for All US Clinical Trials (June 15, 2004), available at [http://www.defending-science.org/upload/AMA\\_2004.pdf](http://www.defending-science.org/upload/AMA_2004.pdf) (calling for mandatory disclosure of all clinical trials results).

195. See FDA, GUIDANCE FOR SPONSORS, INDUSTRY, RESEARCHERS, INVESTIGATORS, AND FOOD AND DRUG ADMINISTRATION STAFF - CERTIFICATIONS TO ACCOMPANY DRUG, BIOLOGICAL PRODUCT, AND DEVICE APPLICATIONS/SUBMISSIONS: COMPLIANCE WITH SECTION 402(J) OF THE PUBLIC HEALTH SERVICE ACT, ADDED BY TITLE VIII OF THE FOOD AND DRUG ADMINISTRATION AMENDMENTS ACT OF 2007 (Mar. 2009), available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125335.htm>.

196. U.S. Nat'l Inst. Health, CLINICAL TRIALS.GOV, <http://www.clinicaltrials.gov> (last visited Jan. 13, 2011).

197. 42 U.S.C. § 282(j)(1)(A)(iii) (Supp. II 2008).

198. *Id.* § 282(j)(3)(A)(ii).

199. Reichman, *supra* note 64, at 40–41.

200. Eisenberg, *supra* note 45, at 384.

201. Bernstein & Bernstein, *supra* note 159, at 600.

202. Cahoy, *supra* note 79, at 625–27. Specific proposals include an evidentiary exclusion from product liability cases for registered studies whose results are fully reported. Additionally, the disclosed study would create a rebuttable presumption that a manufacturer had no prior knowledge of a potential problem should any harms be discovered as a result of the study. *Id.* at 659.

A recent Government Accountability Office (GAO) report recommended that Congress consider expanding FDA authority to require sponsors to conduct postmarketing (Phase IV) studies to collect additional data on the effects of their products.<sup>203</sup> Phase IV trials may be performed for several purposes, including determining optimal dosage, detecting safety problems, evaluating the drug's effects in specific subpopulations such as pediatric or geriatric patients, and identifying "new uses for the product."<sup>204</sup> Such studies are generally not required, although the FDA may seek agreement from an applicant to conduct them in order to address issues that do not preclude approval. In practice, however, the FDA has limited ability to ensure that Phase IV studies are performed.<sup>205</sup>

In select cases the FDA has the authority to require that drug sponsors conduct postmarketing studies as a condition of approval. Whereas the 1988 "fast-track" initiative relied on ostensibly voluntary commitments from manufacturers to perform Phase IV trials, the 1992 "accelerated approval" regulations included mandatory Phase IV requirements.<sup>206</sup> The FDAMA of 1997 ratified FDA's fast-track and accelerated approval regulations "together as one 'fast track' statutory scheme."<sup>207</sup> "While the statutory language affirms FDA's authority to require Phase IV trials pursuant to the accelerated approval regulations [adopted in 1992,] there is some dispute as to whether the provision extends [agency authority to require Phase IV trials] for *any* fast-track drug."<sup>208</sup>

Regulations promulgated in 2002 to allow for the approval of certain drugs merely on the basis of animal testing also included mandatory Phase IV requirements.<sup>209</sup> These "regulations apply only to drugs and biological products that treat or protect against exposure to lethal or permanently-disabling biological, chemical, radiological, or nuclear materials" and were adopted to address the need for countermeasures against "bioterrorism and other forms of nonconventional warfare."<sup>210</sup> In addition, under certain conditions, the FDA can require that drug sponsors conduct post-marketing studies when such studies are needed to provide adequate labeling to ensure the safe and effective use of these drugs in children.<sup>211</sup> Most

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203. U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 38, at 36.

204. Noah, *supra* note 18, at 459.

205. Cahoy, *supra* note 79, at 632-33.

206. Steenburg, *supra* note 99, at 322-23.

207. *Id.* at 330.

208. *Id.*

209. Approval of New Drugs When Human Efficacy Studies are not Ethical or Feasible, 21 C.F.R. §§ 314.600-.650, 601.90-.95 (2010).

210. Steenburg, *supra* note 99, at 328.

211. 21 U.S.C. § 355c(b)(1) (Supp. II 2008). The Pediatric Research Equity Act of 2003 granted the FDA the authority to require drug manufacturers to develop information regarding the safety, effectiveness, dosing, and administration of marketed drugs in children if (1) the drug is used by "a substantial number of pediatric patients for the labeled indications," and the absence of adequate labeling could pose significant risks to pediatric patients; or (2) the drug "would represent a meaningful

recently, in 2007 Congress amended the FDCA to authorize the FDA to require postmarketing studies based on safety information that emerges after a drug's initial approval.<sup>212</sup>

"In the absence of specific authority, FDA often relies on drug sponsors voluntarily agreeing to conduct [postmarketing studies]."<sup>213</sup> Phase IV studies are also performed by drug companies on their own initiative. Such studies are generally part of a strategy to boost sales or ensure insurance coverage, and trials are often planned and designed with specific marketing goals in mind.<sup>214</sup>

The FDA lists basic information about required Phase IV trials in a searchable database available on its website.<sup>215</sup> However, the information about postmarketing studies is located in a different location on the FDA website from information about premarketing studies.<sup>216</sup> Moreover, results of postmarketing trials are subject to the same confidentiality provisions as the results of premarketing studies.<sup>217</sup> Notably, Phase IV studies voluntarily initiated by the drug sponsor are not subject to mandatory public disclosure.<sup>218</sup>

Although postmarketing study commitments are common,<sup>219</sup> sponsor compliance has been poor. A 2004 study found that drug sponsors completed Phase IV clinical trials necessary for upgrading to regular approval in only six of twenty-three fast-track approvals of cancer drugs.<sup>220</sup> Similarly, the Tufts Center for the Study of Drug Development (CSDD) found that only twenty-four percent of agreed upon studies were completed between 1991 and 2003.<sup>221</sup> A report released by the Government Accountability Office in 2009 revealed that from 1992 through 2008, drug makers had completed just two-thirds of 144 requested postmarketing studies on drugs in the accelerated approval program.<sup>222</sup> The high cost of complying

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therapeutic benefit over existing therapies for pediatric patients for . . . claimed indications," or (3) "the absence of adequate . . . labeling could pose [significant] risk[s] to pediatric patients." *Id.* § 355c(b)(1)(A)-(C).

212. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 901(a), 121 Stat. 823, 922-23 (2007).

213. U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 38, at 28.

214. Steenburg, *supra* note 99, at 370-71.

215. Cahoy, *supra* note 79, at 651-652.

216. *Id.*

217. See FDA, GUIDANCE FOR INDUSTRY, REPORTS ON THE STATUS OF POSTMARKETING STUDY COMMITMENTS - IMPLEMENTATION OF SECTION 130 OF THE FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT OF 1997 15 (Feb. 2006), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf>.

218. *Id.* at 4 ("Voluntary studies are not subject to 506B's reporting requirements . . .").

219. See Steenburg, *supra* note 99, at 300 (estimating that nearly eighty percent of recently approved NMEs have faced postmarketing study commitments).

220. Thomas G. Roberts, Jr. & Bruce A. Chabner, *Beyond Fast Track for Drug Approvals*, 351 NEW ENG. J. MED. 501, 501 (2004).

221. Steenburg, *supra* note 99, at 361 (citing TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT IMPACT REPORT, July/Aug. 2004, at 2 [hereinafter TUFTS CSDD STUDY]).

222. Gardiner Harris, *Drug Makers Remain Years Behind on Testing Approved Medicines*, N.Y.

with Phase IV commitments motivates drug companies to evade them.<sup>223</sup> Manufacturers may be “even more reluctant to follow through on FDA-imposed [Phase IV studies], which may sidetrack or undermine postapproval marketing efforts.”<sup>224</sup>

The relative paucity of publicly available Phase IV clinical-trial data has led to calls for expansion of FDA authority over postmarketing studies.<sup>225</sup> However, even if drug companies could be compelled to conduct Phase IV studies, logistical hurdles may be insurmountable. For one, postmarketing developments may make planned Phase IV trials unnecessary or unfeasible.<sup>226</sup> In addition, randomized Phase IV trials possess the same inherent limitations that plague premarketing trials.

Moreover, because Phase IV trials by definition involve products for which preliminary data indicates safety and efficacy, any trial involving a conventional placebo arm poses potentially unacceptable ethical implications for institutional review boards (IRBs).<sup>227</sup> Even if IRB approval can be obtained, it may be impossible to recruit patients into a trial of a marketed drug, as participation in such studies immediately loses its appeal once the drug becomes available in the treatment setting.<sup>228</sup> Indeed, a proposed bill to give the FDA authority to levy fines for failure to perform postmarketing studies was rejected after Senators expressed concerns about the problem of underenrollment in clinical trials and ethical issues involved with denying patients in the control arm of an RCT access to a potentially beneficial new treatment.<sup>229</sup> There may also be political pitfalls involved with proposals to mandate more postmarketing trials, as they would reflect a tacit admission that the approved product may not be safe. “Given the recent attacks on the FDA’s ability to safeguard the nation’s drug and device markets, the agency may be loath to encourage the suggestion that it failed in its job to fully review the product in question before approval.”<sup>230</sup>

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TIMES, Oct. 27, 2009, at A18.

223. The Tufts CSDD recently reported that “the median for *all* Phase IV commitments between 1998 and 2003 was \$3.7 million, even including” relatively low-cost registries and tracking efforts. Steenburg, *supra* note 99, at 370 (citing TUFTS CSDD STUDY, *supra* note 221, at 2). Survey-based studies may cost as much as \$13 million, and “[i]n the case of traditional randomized trials, the sky is the limit.” *Id.*

224. *Id.* at 371.

225. See *e.g.*, Noah, *supra* note 18, at 498 (arguing that Congress should consider authorizing the FDA to mandate Phase IV trials for all newly approved drugs).

226. Indeed, in a report submitted pursuant to the FDAMA, the FDA “acknowledged that thirty-one percent of . . . postmarketing studies for NDAs had turned out to be ‘no longer [necessary] or feasible.’” Steenburg, *supra* note 99, at 342.

227. Steenburg, *supra* note 99, at 372.

228. *Id.* at 372–73.

229. *Id.* at 363–64. Compromise legislation, set forth in section 130 of the FDAMA of 1997, stipulates that manufacturers report annually on the progress of postmarketing investigations and that submitted information be made publicly available to the extent necessary to identify sponsors and status. *Id.* at 364.

230. Cahoy, *supra* note 79, at 670.



*B. Postmarketing Surveillance*

The FDA has adopted a series of measures designed to track unexpected risks of approved products. These include “spontaneous reporting systems to rapidly identify potential new problems; large healthcare databases” about drug use linked to outcomes; observational studies targeted at investigating specific safety issues; and registries created when “potential risks . . . [require] . . . identification and active follow-up of individuals exposed to a product.”<sup>231</sup> However, these are largely reactive endeavors that lack the systematic rigor of the FDA approval process.<sup>232</sup> Moreover, such postmarketing activities are markedly divorced from the agency’s premarketing review and are focused on detecting serious safety problems rather than the broader goal of adding to the compendium of information about a drug’s effects.

FDA postmarketing monitoring involves a system of mandatory reporting of adverse drug reactions (ADRs) by manufacturers and voluntary ADR reporting by health professionals and patients. In response to the information that it receives, the FDA may issue alerts to clinicians, implement labeling changes, or in extreme cases withdraw the product from the market altogether.<sup>233</sup> The FDA does not “require [drug] manufacturers actively to seek out safety information about [the effects of their drugs in the treatment setting].”<sup>234</sup> Firms are only required to submit adverse experience reports that they receive spontaneously from physicians and consumers.<sup>235</sup> FDA regulations require manufacturers to submit quarterly reports of adverse experiences during the first three years of marketing, and annual reports thereafter.<sup>236</sup> The agency’s closer scrutiny during the initial marketing period reflects tacit acknowledgement that much is still unknown about the effects of newly approved drugs.<sup>237</sup>

In 1993, the FDA implemented the MEDWatch Safety system, whereby doctors can electronically submit reports of adverse drug events directly to the agency.<sup>238</sup> This is complemented by the Adverse Event Reporting

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231. Struve, *supra* note 32, at 601 n.60 (citing U.S. DEP’T HEALTH & HUMAN SERVS., FDA, TASK FORCE ON RISK MGMT., MANAGING THE RISKS FROM MEDICAL PRODUCT USE—CREATING A RISK MANAGEMENT FRAMEWORK 54 (May 1999), available at <http://www.fda.gov/downloads/Safety/SafetyofSpecificProducts/ucm180520.pdf>).

232. Struve, *supra* note 101, at 1040 (noting that “in contrast to the rigorous scrutiny of premarketing review, the FDA’s ‘postmarketing surveillance’ program—the means by which the FDA monitors a drug’s safety after its approval—is woefully inadequate.”).

233. Noah, *supra* note 18, at 466–67.

234. *Id.* at 469.

235. *Id.* at 469.

236. See 21 C.F.R. 314.80(c)(2)(i) (2010).

237. Indeed, “[s]ome industry insiders refer to this early marketing period as ‘the red zone.’” Noah, *supra* note 18, at 471.

238. See David A. Kessler, *Introducing MEDWatch: A New Approach to Reporting Medication and Devices Adverse Effects and Product Problems*, 269 JAMA 2765, 2767 (1993).

System (AERS), which receives reports from drug makers.<sup>239</sup> The utility of the information generated is questionable, however, as the system is plagued by underreporting by physicians.<sup>240</sup> Harried clinicians may simply lack the time to diligently submit information about unexpected outcomes.<sup>241</sup> In addition, while short-term ADRs are likely to be detected, individual physicians may not notice an increase in the probability of an event that occurs frequently in the background population.<sup>242</sup> Meanwhile, liability concerns and fears of perceived noncompliance prompt drug companies to over-report potential ADRs, making it difficult to separate true problems from background noise.<sup>243</sup>

The FDA's inability to calculate "the true frequency of adverse events in the population," based on reported outcomes data "makes it hard to establish the magnitude of a safety problem, and it makes comparisons of risks across similar drugs difficult."<sup>244</sup> Since the entirety of the ADR reporting system rests on voluntary submissions, "these reports represent only the proverbial tip of the iceberg of drug reactions and interactions."<sup>245</sup> "[T]he vast majority of reports to . . . [MEDWatch] . . . are unwieldy and unfiltered" and the reports generally do not lead to followup investigations of the patient's medical records.<sup>246</sup> Moreover, the FDA does not have adequate resources to respond promptly and effectively to credible information that it does receive.<sup>247</sup> "[A] 2002 internal survey of reviewers in the FDA's Center for Drug Evaluation and Research (CDER) found that some two-thirds of respondents were either '[n]ot at all confident' or only '[s]omewhat confident' that the CDER 'adequately monitors the safety of prescription drugs once they are on the market.'"<sup>248</sup> The

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239. Related automated reporting programs include the Vaccine Adverse Event Reporting System (VAERS), the Center for Education and Research on Therapeutics (CERTs), and the FDA's Medical Product Surveillance Network (MedSun) pilot program for devices. See Gottlieb, *supra* note 158, at 941.

240. It is estimated that doctors report as few as one percent of all adverse drug events. Anne Trontell, *Expecting the Unexpected—Drug Safety, Pharmacovigilance, and the Prepared Mind*, 351 NEW ENG. J. MED. 1385 (2004).

241. Noah, *supra* note 18, at 479 (noting that "in the era of managed care, reliance on voluntary reporting may be increasingly unrealistic").

242. Struve, *supra* note 32, at 603.

243. See Gottlieb, *supra* note 158, at 940; Struve, *supra* note 32, at 604; Noah, *supra* note 18, at 474–75.

244. U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 38, at 24–25.

245. Noah, *supra* note 18, at 469.

246. O'Reilly, *supra* note 148, at 1082.

247. Despite the recognized deficiencies in postmarketing surveillance, the FDA continues to devote the great majority of its resources to the premarketing review process. See Gardiner Harris, *At F.D.A., Strong Drug Ties and Less Monitoring*, N.Y. TIMES, Dec. 6, 2004, at A1 (noting that the FDA no longer has the resources to fund independent studies of emerging safety issues and that "[i]n the past 11 years, spending on [new drug] reviews has increased to more than four-fifths of the budget of the agency's drug center from about half").

248. Struve, *supra* note 32, at 601 (quoting OFFICE OF INSPECTOR GEN., U.S. DEP'T HEALTH & HUMAN SERVS., HHS SURVEY, at question 45 (2002), [http://www.peer.org/docs/fda/12\\_14\\_04\\_](http://www.peer.org/docs/fda/12_14_04_)

agency openly acknowledges its inability to effectively monitor products after they have entered the market: “Like the proverbial search for a needle in a haystack, the number and variety of products and the lack of reliable usage information, make it difficult to distinguish variability and *noise* from a real concern.”<sup>249</sup>

Several suggestions have been made to rectify deficiencies in the FDA’s surveillance program. Some commentators argue for mandatory pharmacovigilance by drug makers as a condition of continued approval.<sup>250</sup> Another proposal posits that “[t]he FDA should compile information about ADRs from clinical trials, medical records, and computerized databases, including the FDA’s MedWatch database, in one centralized database” and mine the aggregate data to detect potential problems.<sup>251</sup> Several commentators have cast doubt on the FDA’s capability of making meaningful efforts to collect postmarketing data that might refute the agency’s approval decision<sup>252</sup> and have argued for a postmarketing regulatory scheme that comprises both internal FDA personnel as well as outside experts.<sup>253</sup>

“In 2007, Congress directed the [FDA] to create a new postmarketing surveillance system that [would] . . . [utilize] electronic health data . . . to prospectively monitor the safety of marketed medical products.”<sup>254</sup> In response, “[i]n May 2008, the FDA announced the Sentinel Initiative, which would ‘access [a network of] data systems’ . . . [in order] to detect signals . . . and to confirm signals” of safety problems.<sup>255</sup> The statute “created the Reagan-Udall Foundation, a public-private entity through which [the] FDA may carry out the collaborations called for in Sentinel.”<sup>256</sup> This new system is intended to supplement existing spontaneous adverse event reporting mechanisms such as MEDWatch.<sup>257</sup> Sentinel comprises a “distributed network” in which queries are sent to the owners of data, who then

FDA\_survey.pdf).

249. *Id.* at 604 (quoting U.S. DEP’T HEALTH & HUMAN SERVS., *supra* note 231, at 67–68).

250. *See* Bernstein & Bernstein, *supra* note 159, at 591–96.

251. Noah, *supra* note 18, at 500.

252. *See, e.g.*, Phil B. Fontanarosa et al., Editorial, *Postmarketing Surveillance—Lack of Vigilance, Lack of Trust*, 292 JAMA 2647, 2649 (2004) (“It is unreasonable to expect that the same agency that was responsible for approval of drug licensing and labeling would also be committed to actively seek evidence to prove itself wrong (ie, that the decision to approve the product was subsequently shown to be incorrect).”); Struve, *supra* note 32, at 605 (noting that FDA officials are disinclined to identify and expose safety concerns about approved drugs for fear of being proven wrong about their approval decision).

253. *See, e.g.*, Wood et al., *supra* note 167, at 1852 (calling for an independent safety review board devoted to postapproval monitoring of drugs); Steenburg, *supra* note 99, at 381 (arguing that outside involvement is necessary both to counter political pressures on the FDA to ratchet requirements beyond that which is socially optimal and to serve as a check on agency tendencies to ignore preliminary evidence of problems with newly approved drugs).

254. Richard Platt et al., *The New Sentinel Network—Improving the Evidence of Medical-Product Safety*, 361 NEW ENG. J. MED. 645, 645 (2009).

255. *Id.*

256. *Disparate Data Sets Thwart FDA Access to Raw Data in Sentinel*, FDA WK., Dec. 19, 2008.

257. *Id.*

run the queries on their databases and send back results.<sup>258</sup> Notably, the agency “is not given access to the primary data and must rely on the analyses of others.”<sup>259</sup>

Two related pilot projects recently launched by the Centers for Medicare and Medicaid Services (CMS) and the Centers for Disease Control and Prevention (CDC) could serve as models for the FDA’s Sentinel program. The CMS initiated a postmarketing data collection system for the small group of drugs for which the CMS makes national coverage decisions.<sup>260</sup> The system seeks answers to questions such as effects in certain subgroups of patients, effects in settings that differ from those of formal trials, and the risks and benefits of off-label use.<sup>261</sup> The additional evidence collected may allow the agency to make reimbursement for the treatment broader than it otherwise would, because the agency will have more confidence in the individual treatment decisions made by patients and physicians.<sup>262</sup> This of course assumes that appropriate information to guide optimal clinical decision making is adequately analyzed and disseminated into the medical community.<sup>263</sup>

The CDC’s Vaccine Safety Datalink (VSD) project “conducts near-real-time monitoring of new vaccines with the use of a distributed network that combines information from both electronic medical records and administrative databases covering nearly 9 million members of eight health plans.”<sup>264</sup> There are notable logistical challenges involved with implementing such a system, in particular the need to establish uniform, rigorous statistical methods and data-analysis tools.<sup>265</sup> Resources must also be devoted to follow-up investigations, including epidemiologic studies and further clinical trials that may be required to reach definitive conclusions about causation.<sup>266</sup> Commentators have also stressed that

the network’s findings must be communicated in a timely, transparent, and appropriate way to a range of audiences (including health care providers and the public) who are often frustrated by delays in the availability of information related to postmarketing surveil-

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258. *Id.*

259. *Id.* (noting that this decentralized system has led FDA officials to express concerns about the quality of the data and the unreliability of results gleaned from disparate data sets).

260. See CTRS. FOR MEDICARE AND MEDICAID SERVS., DEP’T HEALTH & HUMAN SERVS., DRAFT GUIDANCE FOR THE PUBLIC, INDUSTRY, AND CMS STAFF: FACTORS CMS CONSIDERS IN MAKING A DETERMINATION OF COVERAGE WITH EVIDENCE DEVELOPMENT (2005), available at [www.cms.hhs.gov/coverage/download/guidanceced.pdf](http://www.cms.hhs.gov/coverage/download/guidanceced.pdf).

261. Gottlieb, *supra* note 158, at 945.

262. *Id.*

263. *Id.* at 945–46.

264. Platt et al., *supra* note 254, at 646.

265. *Id.*

266. *Id.*

lance but are also confused about what to do when new (and often not definitive) evidence is made available.<sup>267</sup>

Despite the significant logistical hurdles posed by Sentinel and related initiatives, these efforts represent steps in the right direction for the FDA and other regulatory bodies charged with overseeing the effects of new medical technologies. They represent the agencies' recognition of the significant information gaps that persist under the current regulatory regime. However, these piecemeal efforts do not fully tap the potential wealth of information to be gained from systematic collection of outcomes data. At the same time, there is a danger that Sentinel will simply add another layer of complexity onto an already unwieldy regulatory scheme. Part V of this Article sets forth an alternative regulatory approach whereby prospective outcomes research is seamlessly incorporated into the FDA drug-review process. The proposal arguably achieves a better balance between the desire for innovative progress and the need to protect patient welfare.

## V. PROPOSED REVISION TO THE EXISTING REGIME

### *A. Key Features*

The FDA should develop a regulatory path of earlier market entry coupled with mandatory prospective aggregation of postmarketing outcomes data. This could be achieved through the creation of a centralized database which serves as a clearinghouse of experiential information on the effects of new drugs. The alternative path could begin as a pilot project for new drugs currently eligible for fast-track procedures. Rather than simply extracting Phase IV commitments from sponsors at the time of approval, the FDA would work with manufacturers to formulate a systematic plan for tracking treatment outcomes. This would include identification of specific clinical endpoints and other measures typically delineated in a conventional clinical trial. Prescribing physicians would be required to enter such information into the database. The FDA would play a key role in managing the database by standardizing the format by which data is entered, aggregated, and disseminated.

The agency could build upon this pilot program by expanding the category of drugs eligible for fast-track status to include all drugs whose sponsors agree to enter into the centralized database. Drug manufacturers would make business decisions about whether the downside of partial loss of control over information about their products is outweighed by the upside of reduced hurdles to market. Thus, the proposal mirrors the quid pro quo built into the patent system in that it aims to increase the amount of

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267. *Id.*

publicly available information about proprietary drugs in exchange for competitive benefits. The difference here is that the benefits come in the form of reduced development costs and timelines rather than increased revenues derived from rents. Importantly, sponsors may be more willing to relinquish control over data that is not linked to an FDA approval decision because in this case the information lacks the value premium associated with being a prerequisite for market entry.

This scheme would likely be attractive only for products comprising of true medical breakthroughs, as it would entail persuading patients and treating physicians to utilize drugs based on limited preliminary data under conditions resembling those of a formal clinical trial. Thus, as with products currently eligible for fast-track designation, appropriate drugs would aim to treat serious conditions for which few treatment options exist. However, the category of drugs elected by sponsors for entry into this alternative regulatory scheme could potentially be somewhat broader than that currently allowed by the FDA into the fast-track program.

Pharmacosurveillance activities could be funded by drug sponsors as a set percentage of revenues derived from sales of the tested drug. This would ensure that the costs incurred by the manufacturer correlate with the extent of drug utilization and the corresponding amount of required monitoring. Additionally, PDUFA fees could be set aside in order to compensate physicians for reporting outcomes and for data aggregation and analysis. Perhaps the costs associated with postmarketing surveillance could be borne in part by private and public payers who have incentives to fund the generation of the information necessary to ensure informed treatment decisions. CMS could lead the way in this regard by adequately reimbursing prescribing physicians for their participation in the systematic collection of outcomes data.

The proposed scheme would capture a broader range of information than that currently gathered by MEDWatch and related databases. In addition to ADRs, it would generate more nuanced information such as dose-response data and the identification of particular patient populations for which the drug is effective. This system might also lead to the more rapid identification of new uses for monitored drugs, as it would more efficiently harness information about utilization beyond the primary indication than does the current practice of off-label use. Since the database would track both unexpectedly positive outcomes as well as negative outcomes, it would expose manufacturers to both downside risk and upside potential.

Postmarketing monitoring through an FDA-administered centralized database would help to collapse the artificial distinction between the experimental and treatment phases of new drugs.<sup>268</sup> “Whether we know it or

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268. See Noah, *supra* note 2, at 362–63 (noting that drug approval “does not define the point at

not, and whether we like it or not, all patients are subjects in medical research.”<sup>269</sup> The systematic collection of outcomes data for newly marketed drugs would serve as an extension of the clinical testing performed in the premarketing stages. Under this approach, entry onto the market would be viewed as simply a point on the continuum of clinical research on the effects of the drug rather than a sharp dividing line between investigational and standard therapy.

This scheme would help to rationalize the market for information about new drugs by allowing individual patients to stratify themselves based on the value that they place on safety and efficacy data. Some patients may be more willing to accept information gaps than others, and thus be willing to take newly marketed, relatively untested drugs. Others may demand more information, and thus will decline the drugs until more information is generated through the ongoing collection of prospective outcomes data as well as any formal studies undertaken by the drug manufacturers and others. This is not unlike the current decision faced by patients eligible to enroll in premarketing clinical trials. The difference here is that the patient is guaranteed to receive the drug to be tested, and the drug is available to all comers, not just patients fitting narrowly circumscribed criteria.

The proposal takes a market-based approach in that it aims to increase the quantity and quality of publicly available drug safety and efficacy data so as to enable physicians and doctors to make informed treatment decisions. The goal is to attenuate the problem of imperfect information by increasing transparency and improving the knowledge base of the drug consumers (patients) and their proxies (physicians). This is achieved through the voluntary actions of product manufacturers making rational decisions about the net benefits of opting for earlier market entry under the outlined parameters. This is in contrast to possible alternative approaches which would address information gaps with increased agency intervention, such as mandating additional Phase IV testing as a condition of approval.

The FDA’s permissive policy towards off-label use tacitly acknowledges the existence of inevitable information gaps regarding the effects of approved drugs and the benefits derived from experimentation by physicians in the treatment setting.<sup>270</sup> Rather than rigidly separating the premarketing review process from such postmarketing innovation, the proposed

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which an investigational intervention passes the threshold into standard therapy. Instead, the research phase continues after licensure, both in the sense that more safety data accumulates and insofar as physicians may improvise when using a product in ways not originally contemplated. Conversely, an investigational product may become the standard of care even before federal regulators bestow their blessing on a particular use”).

269. *Id.* at 408.

270. *Id.*

scheme calls for the FDA to adopt a more fluid approach to drug regulation centered on information generation. It compels the agency to formally recognize the importance of outcomes data, not merely as a means to identify potential adverse events, but also as a mechanism for complementing the efficacy data derived from RCT.

### *B. Comparative Advantages*

This alternative regulatory path builds upon existing programs to shift the FDA's role from market gatekeeper to facilitator of information consolidation and dissemination. The agency would use its regulatory authority not to hold potentially promising products hostage but rather to foster the release of information that drug companies may not otherwise generate and disclose to those seeking it (i.e., patients, doctors, and payers). At the same time, it would reduce development costs and promote faster entry of innovative products onto the market.

Systematic reporting by clinicians in the course of treating their patients would reduce FDA reliance on drug sponsors to complete Phase IV studies. Greater assurance of the generation of comprehensive, reliable postmarketing data should attenuate bureaucratic conservatism. The proposed shift in regulatory focus could therefore serve to recharge stalled fast-track programs and quicken the pace of biomedical progress. It would also obviate the need to contort the regulatory process with convoluted expanded-access regulations, since the distinction between investigational and standard therapy generally collapses under this scheme.

Drug companies' selection of the proposed regulatory option could serve as a signal of confidence in the drugs' safety and efficacy because it demonstrates the sponsor's willingness to relinquish partial control over the production and dissemination of information about its products. The argument that FDA approval solves the "market for lemons" problem by assuring the quality of new drugs<sup>271</sup> is compelling in the abstract but does not accord with the scientific reality that the results of FDA-mandated RCT often fail to accurately predict the safety and efficacy of drugs in the treatment setting. RCT rarely yield clear answers about the expected effects of drugs in the general population, as evidenced by the strong disagreements that frequently arise between FDA reviewers tasked with making approval decisions.

Equating FDA approval with a certification of quality thus risks further distortion of the market for information about drug safety and efficacy. Patients and physicians may give more credence to FDA approval than is warranted, which may lead to suboptimal treatment decisions. Drug

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271. Katz, *supra* note 7, at 11–12.



companies' willingness to participate in a more open regulatory scheme may be a better signaling mechanism than the FDA stamp of approval, since manufacturers know most about their proprietary products. Sponsors themselves may find benefits in a more open system in which the FDA no longer acts as the gatekeeper of the data generated, as it would entail less uncertainty and reading of tea leaves with respect to how the FDA will respond to trials results and convey that information to end users. The proposed alternative regulatory scheme may be particularly attractive to small and mid-sized companies which lack sufficient capital to complete premarketing trials on their own and otherwise would need either to be acquired or to form a strategic partnership with a larger company in order to bring their products to market.

Reducing the time to market entry should also reduce pressures to create exclusivity grants beyond those provided by the patent system.<sup>272</sup> Currently, manufacturers protect the products themselves with patents but protect relevant clinical-trial data through trade secrets and related mechanisms. If firms can be induced to treat their clinical-trial data more like they treat other information about their products—that is, voluntarily make it publicly available in exchange for competitive benefits—there will be less discordance between the patent and regulatory systems. Moreover, there will be fewer complicated overlaps between the functions and roles of the two systems in promoting biomedical innovation.

The proposed database would provide quantitative data derived from the collective anecdotal experiences of individual physicians, thereby enhancing the traditional approach to the aggregation of medical knowledge through the use of modern information technology. As such, the data generated may be more persuasive to those clinicians who harbor reservations about the utility of clinical trials. Commentators have observed that the costs of FDA review come in the form of both higher pharmaceutical prices and the loss of “phantom products” that would have been developed but for the burdens of regulation.<sup>273</sup> An additional cost of the FDA's predominate focus on premarketing review is the loss of “phantom” experiential information that is not effectively captured in the treatment setting. Systematic tracking of patient outcomes with new drugs would serve to harness and disseminate this information. This changes the calculus in the trade-off between the benefits of generating additional safety and efficacy data prior to market entry and the costs of delaying access to new therapies.

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272. This has implications for the debate over the proper period of exclusivity for brand name biologics which will face generic competition from “biosimilars” under proposed legislation. *See, e.g., Andrew Pollack, Costly Drugs Known as Biologics Prompt Exclusivity Debate*, N.Y. TIMES, July 21, 2009, at B1, available at <http://www.nytimes.com/2009/07/22/business/22biogenerics.html?partner=rss&emc=rss>.

273. Greenberg, *supra* note 96, at 664.

### C. Potential Criticisms and Responses

Earlier market entry raises evident safety concerns, particularly with respect to drugs not currently eligible for fast-track status which are presently required to undergo extensive premarketing testing. In order to protect the welfare of patients in the treatment setting, measures would need to be taken analogous to those taken during RCT. Informed-consent rules should be implemented which mirror those for RCT.<sup>274</sup> Patients should be made aware that they are essentially subjects in the postmarketing phase of ongoing experimentation with the new drug. In addition, postmarketing surveillance would include ongoing monitoring to look for clear patterns suggesting a serious problem with the drug. Where such patterns emerge, the FDA would retain authority to mandate additional formal trials to investigate potential problems.

Arguably, systematic postmarketing surveillance in the treatment setting is a safer course for patients than enrollment in RCT, since in this case the patient is not at risk of receiving a placebo and facing no chance of personal benefit. It may also be safer than the current practice of off-label use, since under the proposed scheme patients would be systematically monitored. Thus, trends may become apparent more quickly than they now do through the comparatively haphazard diffusion of medical knowledge about unapproved uses of marketed drugs.

A related concern involves the loss of socially valuable information about new drugs that would otherwise be generated through FDA-mandated Phase III and Phase IV trials. The proposed database would admittedly be less precise and more open to subjective interpretation than traditional RCT.<sup>275</sup> It should be designed not to replace entirely the conventional approach, but rather to supplement designed trials in order to

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274. See Allan Brett & Michael Grodin, *Ethical Aspects of Human Experimentation in Health Services Research*, 265 JAMA 1854, 1856–57 (1991) (discussing the role of informed consent in prospective-outcomes research). See also Noah, *supra* note 2, at 404 (noting that epidemiologists generally must secure informed consent before including individuals in a database or performing follow-up on diagnostic work).

275. Conventional alternatives to RCT include (1) case reports or series, adverse event reports, and other anecdotal evidence; and (2) observation studies in which the researcher does not assign subjects to treatment and control groups. The former types of evidence cannot be used to establish causation because they lack control groups. See David H. Kaye, David A. Bernstein & Jennifer L. Mnookin, *The New Wigmore on Evidence* (2d ed. 2011). Observational studies detect correlations but generally are less capable than RCT to definitively establish causation. *Id.* When a well conducted and reasonably powerful RCT conflicts with a well conducted observational study, the consensus among epidemiologists is to trust the RCT. See, e.g., Stuart Barton, *Which Clinical Studies Provide the Best Evidence? The Best RCT Still Trumps the Best Observational Study*, 321 Brit. Med. J. 255 (2000). Thus, when it comes to confirming causation, RCT remain the statistical gold standard. For more on the feasibility of relying on data-mining to establish causation, see I Ahmed, F Thiessard, G Miremont-Salamé, B Bégau, and P Tubert-Bitter, *Pharmacovigilance Data Mining With Methods Based on False Discovery Rates: A Comparative Simulation Study*, 88 *Clinical Pharmacology & Therapeutics* 492–498 (2010); Bradley Efron, *Size, Power and False Discovery Rates*, 35 *Annals Stat.* 1351 (2007).

develop more comprehensive safety and efficacy profiles for new drugs. Harnessing clinicians' experiential knowledge should both reduce pressure on the FDA to mandate more premarketing testing data than is socially desirable and counteract the incentives of drug companies to disseminate incomplete or misleading information.

If patients and physicians cannot be sufficiently persuaded to utilize a marketed drug based on available preliminary data, drug companies will be compelled to voluntarily conduct formal trials. In addition, trends observed from postmarketing surveillance could prompt follow-on studies of suspected effects by drug sponsors and interested third parties such as the National Institutes of Health (NIH). It would be dangerously naïve to suggest that fast-track market entry followed by postmarketing tracking of clinical outcomes is appropriate or sufficient in all cases. Rather, the proposed alternative regulatory scheme is envisioned to operate most frequently and most effectively in those cases in which demands for expanded access currently come into play.

The proposed scheme presents additional challenges to physicians already struggling with information overload.<sup>276</sup> The medical community has a poor track record of incorporating newly discovered information about marketed drugs into its treatment decisions.<sup>277</sup> Physicians, medical societies, and other interested parties must be willing to take on a more proactive role in assessing the relative merits of innovative products. A period of adjustment would be expected as the stakeholders learn how best to digest and synthesize the information that is generated. The FDA should allow access by designated, certified third parties (e.g., qualified health services research firms) to the raw postmarketing data. These entities could provide analyses which are easily accessible to patients and physicians on the FDA website.

The additional postmarketing data that is generated could potentially expose drug manufacturers and physicians to increased risk of tort liability. Mechanisms must be instituted which preserve legitimate tort claims but also prevent the database from becoming a data mining tool for plaintiffs' attorneys with incentives to muddle and distort the information for their own gain at the expense of drug manufacturers and ultimately the consumers of their products. Drug makers should be held liable for failing to warn of effects that become apparent from outcomes data, but should not be unduly burdened with the expectation to provide real-time communication of information as it is generated. In addition, measures must be

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276. Noah, *supra* note 28, at 404.

277. *Id.* at 438–39 (citing a recent study by the FDA which found that labeling revisions and other efforts to communicate to clinicians new safety information about a popular heartburn remedy had essentially no impact on prescribing behavior). *See also* Walter Smalley et al., *Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action*, 284 JAMA 3036, 3039 (2000).

taken to ensure that physicians who prescribe new medications are not exposed to excessive liability for failure to warn of risks that are revealed through systematic postmarketing surveillance. This could be achieved through the adoption of evidentiary exclusion rules which place reasonable limits on use of the data in products liability and medical malpractice litigation.

Systematic collection of outcomes data threatens to exacerbate concerns over patient privacy.<sup>278</sup> Data entry by physicians should be anonymized, but it may be necessary to review actual medical records when preliminary data mining suggests a clinically significant pattern. Again, informed consent is paramount. Patients must be made aware of and comfortable with this possibility, and care must be taken to minimize undesirable consequences.

Finally, the proposed scheme may face political resistance by those who see it as partial abdication of FDA responsibility. The proposal does not entail a reduction in agency authority, but rather a reallocation of FDA resources. Inescapably, however, this may lead to internal rancor within the agency. Moreover, this initiative should be framed as a source of patient and physician empowerment, and a means to capture the potential of the information age.

## VI. CONCLUSION

The legislative history of the 1962 Amendments indicates that their proponents were highly skeptical of physicians' abilities to effectively absorb the vast amount of information about new medical technologies. Their solution was to shift responsibility for gathering and deciphering such information from doctors to the FDA, at least with respect to the initial indication for which manufacturers seek marketing approval. This is not the optimal regulatory scheme. Rather, we should harness modern information technology to facilitate a more dynamic regulatory approach which acknowledges the false dichotomy between experimentation and treatment.

The 1962 amendments were adopted during a period in which the scientific community embraced the RCT as the means for methodically and accurately establishing the safety and efficacy of new drugs. Recently, however, there has been a reexamination of the capability of RCT to provide the information necessary for patients and physicians to make informed treatment decisions. The inherent limitations of RCT call into

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278. See, e.g., Milt Freudenheim, *And You Thought a Prescription Was Private*, N.Y. TIMES, Aug. 8, 2009, at BU1, available at [www.nytimes.com/2009/08/09/business/09privacy.html](http://www.nytimes.com/2009/08/09/business/09privacy.html) (highlighting privacy concerns involved when companies buy and sell electronic personal medical data without patients' consent).

question the determinative role that RCT plays in the decision to approve new drugs for entry onto the market. At the same time, there is growing recognition of the potential of modern information technology to capture valuable experiential data about the use of newly approved drugs. The systematic collection and synthesis of postmarketing data into a readily digestible form could significantly improve physicians' and patients' ability to make rational, risk-benefit treatment decisions.

Both the FDA and the general public must come to terms with the "Hobson's choice" of medical innovation, and acknowledge that every new drug enters the market with substantial information gaps about its safety and efficacy. The much debated trade-off between access on one hand and public safety on the other is largely illusory. While RCT can provide valuable statistical information about a specific population of subjects, no amount of formal testing will enable clinicians to confidently predict how individual patients will respond to a new treatment. Although this fact is generally acknowledged, the notion stubbornly persists that drugs which have successfully undergone the extensive testing mandated by the FDA approval process should be safe and effective, and if they turn out to have unexpected effects in the general population then the FDA must have made the wrong decision.

The approach set forth in this Article attempts to straddle the ideological divide between those who advocate for increased FDA-mandated data production and disclosure and those who argue that patients should be allowed to assume the risk of incomplete safety and efficacy information. Such risk is unavoidable, but there is a role for the FDA to proactively intervene to attenuate that risk by illuminating information gaps and gathering prospective outcomes data about the effects of new drugs.

Perhaps in the past it was justifiable for the FDA to keep novel products off the market prior to completion of extensive formal testing. But now we have the tools to effectively capture and analyze information about clinical experiences with new drugs. The systematic collection and dissemination of anecdotal information would greatly enhance its value. This alters the calculus when weighing the relative value of the information that is generated from controlled premarketing trials with the potential social benefits of earlier entry to market.

The justification for extensive FDA-mandated, premarketing testing is that the associated costs—fewer innovative products, higher prices, and delayed access for individuals who are not eligible for clinical trials and do not satisfy the stringent requirements for expanded access—are outweighed by the benefits derived from RCT that would not otherwise be performed. This argument loses force, however, when one acknowledges the limitations of RCT. It further weakens when one considers the potential informational value created by a system of comprehensive postmarketing surveillance. A scheme of earlier market entry of new drugs coupled with

enhanced collection of treatment outcomes will yield net social benefits. It will not eliminate the inevitable risks associated with new medical technologies, but it has the potential to empower patients to make better informed decisions about their care.

The failed promise of the “fast-track” programs serves as a case study demonstrating the pitfalls of the agency’s assumed role of guarantor of drug safety and efficacy. It creates an inherently unachievable task, the difficulties of which have become magnified as the pace of innovation in biomedical research has intensified. Releasing the FDA from the burden of the mantle of guarantor of patient welfare is necessary if the agency is to successfully facilitate access to patients and clinicians to optimal information about the effects of new drugs.

In order to effectuate meaningful change, any proposed improvements to the current regulatory regime will need to coincide with a recognized revision of the mission of the FDA. This Article proposes that the FDA go “back to the future” with a twist. The agency should focus on its original aim of preventing the spread of false claims and misinformation by harnessing the tools of the twenty-first century to promote consolidation and dissemination of information gleaned from the treatment setting.

Inevitably, the raw data generated by the proposed postmarketing monitoring system will engender debate with respect to the conclusions to be drawn from their interpretation. This is an essential aspect of scientific inquiry, and is especially prominent in the area of biomedical research. The fact that there are rarely uncontested opinions about the proper treatment course for a particular disease, let alone an individual patient, underscores the problem with the binary approval–disapproval determination adopted by the FDA. A preferable approach is to openly acknowledge the inherent uncertainties attendant to new medical technologies and to act to attenuate those uncertainties with the tools that are available. The proposed scheme will often fail to yield clear answers about the safety and efficacy of new drugs, but should lead to more rational decision making by patients and physicians.