

## THE ROLE OF THE FDA IN INNOVATION POLICY<sup>†</sup>

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The history of the U.S. Food and Drug Administration (FDA) has been punctuated by periods of growth and retrenchment as the political climate for regulation has responded to events, interest groups, and ideology. Over the past century, Congress has repeatedly expanded the FDA's legal powers in response to popular pressure for regulation following a public health crisis,<sup>1</sup> and then tightened the agency's leash in

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1. This history is recounted in detail in PHILIP J. HILTS, *PROTECTING AMERICA'S HEALTH: THE FDA, BUSINESS, AND ONE HUNDRED YEARS OF REGULATION* (2003) and sources cited therein. Congress was driven to pass the original Food and Drug Act of 1906 by public outcry following the publication of a series of magazine articles exposing fraudulent and dangerous practices by sellers of "patent medicines" and of Upton Sinclair's novel, *The Jungle*, exposing unsavory practices in the food industry. *Id.* at 46–55. A few years earlier, Congress had passed the Biologics Act of 1902 following outbreaks of infections and some deaths from sales of contaminated batches of antitoxin and vaccines. *Id.* at 68–69. Passage of the Food, Drug, and Cosmetic Act of 1938, which expanded the FDA's authorities to require proof of safety before drugs could be marketed, followed the deaths of over 100 patients (mostly children) from ingesting a lethal batch of sulfanilamide, one of the first antibiotics. *Id.* at 89–93. Congress further expanded the FDA's authorities to require proof of efficacy as well as safety in 1962, with passage of the Kefauver-Harris amendments to the Food, Drug, and Cosmetic Act, in the face of public alarm following births of children with deformed limbs whose mothers had been given thalidomide to prevent miscarriage (a use for which the drug was ineffective). *Id.* at 144–65. In each of these instances, the legislative reform initiative gained a crucial boost from public alarm over a recent crisis to overcome what had previously seemed like insurmountable opposition.

Congress currently faces proposals to expand the FDA's authority with regard to post-approval clinical trials and labeling changes in the wake of revelations concerning the cardiovascular side effects of Vioxx. *See, e.g.*, The Enhancing Drug Safety and Innovation Act of

response to pressure from industry and opponents of regulation during periods of ascendancy for free market ideology.<sup>2</sup> Throughout this period the most politically compelling arguments in favor of regulation emphasized public health and the protection of patients from unknown hazards, while the most compelling arguments against regulation emphasized the interests of patients and doctors in making their own therapeutic choices unfettered by government regulation.<sup>3</sup>

A different set of tradeoffs has figured in the debate about drug patents. The pharmaceutical industry, lobbying for stronger patent laws throughout the world, has sung the praises of the patent system as a means of promoting costly and risky investments in research and development (“R&D”). In contrast, public health advocates, calling for restrictions on patent rights, have stressed the importance of improving access to drugs for people who otherwise cannot afford them.<sup>4</sup> When drug regulation is mentioned in these debates, it is typically invoked by the patent advocates, who cite it as a large part of the cost of drug development that can only be recovered if firms are allowed to charge patent-protected premium prices for new products. This framing suggests a symbiotic tension between patents and drug regulation: patents protect the rents that make drug regulation affordable to innovating firms, while the public health imperative for regulation fortifies the justification for patent protection. It also suggests that the public health goals that justify drug regulation are in competition with the innovation goals that justify the patent system. In this picture, patents promote innovation by making it profitable, while drug regulation deters innovation, in furtherance of the competing goal of public health, by making it costly.

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2007, S. 484, 110th Cong. (introduced Feb. 1, 2007); Food and Drug Administration Safety Act of 2005, S. 930, 109th Cong. (introduced Apr. 27, 2005).

2. Again, Hiltz provides a comprehensive summary of the past century of opposition to FDA regulation, including, within recent memory, the efforts of the Office of Management and Budget in the Reagan administration in the 1980s, HILTZ, *supra* note 1, at 210–54, and of the House Republicans under the leadership of Newt Gingrich in the 1990s. *Id.* at 295–331. These efforts have typically been more successful in curtailing the resources available to the FDA than in curtailing its legal authorities, although a notable exception was passage of the Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103-417 (codified as amended at scattered provisions of 21 U.S.C.), which limits the authority of the FDA to regulate dietary supplements, vitamins, and herbal remedies sold for therapeutic purposes.

For different historical perspectives, see PETER TEMIN, *TAKING YOUR MEDICINE* (1980); JOHN ABRAHAM, *SCIENCE, POLITICS AND THE PHARMACEUTICAL INDUSTRY* (1995); Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753 (1996).

3. For a recent articulation, see *Abigail Alliance v. Von Eschenbach*, 445 F.3d 470, *vacated*, 469 F.3d 129 (D.C. Cir. 2006).

4. See, e.g., Shanker A. Singham, *Competition Policy and the Stimulation of Innovation: TRIPS and the Interface Between Competition and Patent Protection in the Pharmaceutical Industry*, 26 BROOK. J. INT'L L. 363 (2000).

Framing the relationship between patents and drug regulation in this manner is seriously incomplete and out of date. It misses the important structural role that drug regulation has come to play in *promoting* a valuable form of pharmaceutical innovation—the development of credible information about the effects of drugs. If a century ago the goal of drug regulation was to protect people from poisons, today drug regulation guides the development of information that turns poisons, used advisably, into drugs.

Empirically tested knowledge about effects in patients is what distinguishes the products we call “drugs” from similar products sold in minimally regulated markets, sometimes for similar purposes (including many of the products sold on the shelves of health food stores). Creating new molecules has become easier with new technologies, but determining which molecules are safe and therapeutically effective remains stubbornly expensive, time-consuming, and risky. Information about drug effects is an extremely valuable resource for guiding sound therapeutic choices, as well as for guiding the development of better products in the future. For the most part, we rely on drug-developing firms to produce this information. There is good reason, however, to worry about the motivation of firms to supply this information in an unregulated market. In addition to the spillover problems that dampen R&D incentives for many information-enriched products, market incentives to generate rigorous information about the effects of drugs are distorted by the risk that better information could as readily undermine the commercial value of the products under study as enhance it.<sup>5</sup> Pharmaceutical firms sell drugs rather than selling information as such, and they face powerful incentives to cheat in developing and selectively disclosing information about their products in order to improve sales. Inducing firms to provide high quality information about the effects of drugs in patients is thus a major challenge for regulators.

FDA regulation has also become an important adjunct to the patent system in protecting innovating firms from competition in product markets. The most effective regulatory power that the FDA has over the pharmaceutical industry is its premarket approval authority,<sup>6</sup> which permits the FDA to keep new products off the market pending proof of

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5. Recent examples include revelations about the cardiovascular effects of some Cox-2 inhibitors (including Vioxx) and the effects of hormone replacement therapy in postmenopausal women, discussed in greater detail below. Of course, even negative information about the effects of drugs is socially valuable, but this social value may not be captured by a firm that relies on sales of drugs to recoup its investment in generating the information.

6. Federal Food, Drug, and Cosmetic Act § 505 (codified as amended at 21 U.S.C. § 355).

safety and efficacy.<sup>7</sup> Although premarket approval is understood primarily as a consumer protection measure, in the past twenty years Congress has repeatedly fine-tuned the FDA's mandate as a market gatekeeper in ways that might be better understood in terms of innovation policy, calibrating the balance of costs and incentives for both innovating firms and generic competitors. The effect has been to blur the distinction between patents and FDA regulation as determinants of the duration of lucrative exclusivity in pharmaceutical product markets. FDA regulation, like patent protection, confers valuable exclusionary rights as a reward for investing in certain kinds of R&D, thereby adding to both the profits and costs of drug development.

Indeed, as the role of the patent system in drug development has become more complex and ambiguous, drug regulation has become an increasingly important source of market exclusivity for innovating firms. Although the pharmaceutical industry has long been famously dependent upon patents, the term of patent protection is far from optimal for the purpose of securing rents from sales of patented drugs. Basic "composition of matter" patents<sup>8</sup> on drugs are typically issued in the early stages of product development, before the effects of these molecules have been tested in clinical trials. Much (or even all) of the term of these initial patents may have expired by the time the products are brought to market,<sup>9</sup> leaving firms to look elsewhere for protection from generic competition. This problem has been aggravated by the switch in expiration date for U.S. patents from seventeen years from the issue date to twenty years from the filing date,<sup>10</sup> although it is mitigated by special provisions for patent term extension available for drug patents.<sup>11</sup> In recent years firms have become quite creative about strategies to secure "evergreening"

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7. Although generic versions of previously approved products are also considered new drugs that require FDA approval, the standard for approval of generic versions of previously approved products is easier (and cheaper) to meet than the standard for a pioneer product. Compare 21 U.S.C. § 355(b) (requirements for approval of pioneer product) with § 355(j) (requirements for approval of generic product).

8. The statutory categories of patentable subject matter under U.S. law include "any new and useful process, machine, manufacture, or composition of matter." 35 U.S.C. § 101.

9. A notable recent example is Paxil, an antidepressant that did not get to market until the original patent on the molecule had expired. The manufacturer obtained additional patents on different versions of the molecule, but was ultimately unsuccessful in its efforts to use these patents to stop generic competition. It nonetheless enjoyed a significant period of market exclusivity before the FDA could entertain an abbreviated new drug application (ANDA) from a generic competitor. See *infra* note 27 and accompanying text.

10. Pub. L. No. 103-465, 108 Stat. 4809 (1994) (codified in pertinent part at 35 U.S.C. § 154(a)(2)).

11. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, tit. II, 98 Stat. 1585, 1598 (1984) (codified in pertinent part at 35 U.S.C. § 156).

patents in order to defer the date their products go off-patent,<sup>12</sup> but the industry has had limited success in persuading the courts to enforce these patents against generic competitors.<sup>13</sup> Meanwhile, patents have played an expanding role in the early stages of biomedical research, leading to a proliferation of patents on research discoveries that lie upstream of pharmaceutical end-product development.<sup>14</sup> These upstream patents are more likely to add to the costs of drug development than they are to add to its profits.

This Article reexamines the role of FDA regulation in motivating investment in biopharmaceutical innovation. I begin by challenging the standard story that it is the patent system that makes drug development profitable, and drug regulation that makes it costly, by showing how patents add to costs and how drug regulation works in tandem with patents to protect profits. I then compare FDA-administered exclusive rights to patents as a means of fortifying drug development incentives, suggesting ways that FDA-administered rights might be preferable both from the perspective of policy makers and from the perspective of firms. In the remainder of the Article, I turn to the role of the FDA in regulating clinical trials of new drugs, reconsidering its regulatory functions from the perspective of innovation policy (i.e., motivating the provision of information about drugs) rather than from the more conventional perspective of protecting health and safety (i.e., keeping unsafe products off the market). Some aspects of the current regulatory scheme, such as keeping products off the market and limiting permissible marketing claims pending the completion of clinical trials, make more sense from this

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12. Lara J. Glasgow, *Stretching the Limits of Intellectual Property Rights: Has the Pharmaceutical Industry Gone Too Far?*, 41 IDEA 227 (2001).

13. See, e.g., *Schering Corp. v. Geneva Pharm.*, 348 F.3d 992 (Fed. Cir. 2003) (holding patent on metabolite of popular drug loratadine invalid under doctrine of anticipation by inherency); *Geneva Pharm. v. GlaxoSmithKline*, 349 F.3d 1373 (Fed. Cir. 2003) (holding later-issued patents deriving from same parent application as expired patent invalid under doctrine of double patenting); *Zenith Labs. v. Bristol-Myers Squibb*, 19 F.3d 1418 (Fed. Cir. 2003) (finding no infringement of patent on metabolite of antibiotic cefadroxil because of failure of proof that patients were making patented metabolite after ingesting off-patent drug); *Smith-Kline Beecham v. Apotex Corp.*, 365 F.3d 1306 (Fed. Cir. 2004) (holding patent on "hemihydrate" form of drug, which patentee alleged was infringed when patients given older "monohydrate" form converted the drug to the hemihydrate following ingestion, invalid on grounds of prior public use in the course of clinical trials), *vacated*, 403 F.3d 1328 (Fed. Cir. 2005), *superseded*, 403 F.3d 1331 (holding same patent invalid on ground that prior patent disclosing administration of drug to patients inherently anticipated claim to hemihydrate form).

14. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 249 F. Supp. 2d 216 (W.D.N.Y. 2003), *aff'd*, 358 F.3d 916 (Fed. Cir. 2004), *reh'g & reh'g en banc denied*, 2004 U.S. App. LEXIS 13784 (Fed. Cir. 2004) (unsuccessful effort to enforce patent on selective inhibition of Cox-2 enzyme without inhibiting Cox-1 enzyme against firms that had developed selective Cox-2 inhibitors).

revisionist perspective than they do from the conventional perspective. Yet other aspects, such as the relative emphasis on pre-approval studies over post-approval studies and the FDA-enforced secrecy of clinical trial data, come in for new criticisms and suggest new questions for scholars and policy makers.

## I. THE CHANGING ROLE OF PATENTS IN DRUG DEVELOPMENT

Biopharmaceutical research is often held out as a shining example of the success of the patent system in motivating private investment in R&D. The business of drug development is characterized by unusually large spending on research by the standards of other industries.<sup>15</sup> Biomedical research makes up a large part of overall R&D spending in both the public and private sectors, and it is an area in which empirical studies have found that patents really seem to matter.<sup>16</sup> The pharmaceutical industry has long and ardently maintained that patents on drugs are crucial to the financial viability of drug development.

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15. A 2001 study from the industry-funded Tufts Center for the Study of Drug Development estimates average costs to develop a new drug at \$802 million, using self-reported data and applying a discount rate of 11% to capitalize average out-of-pocket costs of \$403 million to the point of marketing approval. See Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151 (2003). Critics immediately challenged this estimate as inflating the true costs. See Press Release, Public Citizen, *Tufts Drug Study Sample Is Skewed; True Figure of R&D Costs Likely Is 75 Percent Lower* (Dec. 4, 2001), available at <http://www.publiccitizen.org/pressroom/release.cfm?ID=954>; Ceci Connolly, *Price Tag for a New Drug: \$802 Million: Findings of Tufts University Study Are Disputed by Several Watchdog Groups*, Washington Post, Dec. 1, 2001, at A10. See also MERRILL GOOZNER, *THE \$800 MILLION PILL: THE TRUTH BEHIND THE COST OF NEW DRUGS* (2004).

A 2003 Bain & Co. study estimated the average costs of drug development at more than twice the number calculated in the Tufts study, citing declining R&D productivity, rising costs of commercialization, increasing payor influence, and shorter exclusivity periods. See Jim Gilbert et al., *Rebuilding Big Pharma's Business Model*, 21 IN VIVO: BUS. & MED. REP. 10, Nov. 2003, available at [http://www.bain.com/bainweb/PDFs/cms/Marketing/rebuilding\\_big\\_pharma.pdf](http://www.bain.com/bainweb/PDFs/cms/Marketing/rebuilding_big_pharma.pdf). These cost estimates, which include R&D costs of failed products as well as those directly attributable to successful products, are highly sensitive to the success rate for candidate products, rising when the success rate declines. The recent dearth of successful new products for the pharmaceutical industry thus inevitably increases the calculated costs per product.

16. Empirical studies indicate that this is an area where decision-makers really care about patents when they contemplate spending money on R&D, in contrast to other fields and industries that rate other, non-patent factors as more important. Wesley M. Cohen et al., *Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent (Or Not)* 1–31 (National Bureau of Econ. Research, Working Paper No. 7552, 2000), available at <http://www.nber.org/papers/W7552.pdf>; Richard C. Levin et al., *Appropriating the Returns from Industrial Research and Development*, 3 BROOKINGS PAPERS ON ECON. ACTIVITY 783 (1987).

There are signs, however, that the patent system is not working as well as it used to for the pharmaceutical industry. A fundamental problem with patent protection for new drugs has to do with timing. Historically, the most valuable patents on drugs have been “composition of matter” patents that cover the drug molecule itself, without limitation as to use. Such patents may be enforced against competitors who make, use, sell or import the same product for any purpose throughout the patent term.<sup>17</sup> Patents on particular methods of treatment involving the use of a drug are generally considered less valuable, because they cannot be used to stop competitors from selling the same product for other uses.<sup>18</sup> In theory, the patent holder could still enforce the patent against patients who use the product for the patented use, against doctors who prescribe it for such use, against pharmacists who fill the prescriptions, or against manufacturers who urge any of these actors to substitute bioequivalent products for the patent holder’s product in such prescriptions.<sup>19</sup> But remedies against customers and intermediaries are generally considered less satisfactory than an injunction against a competitor that will stop it from making the product entirely.<sup>20</sup>

Despite the advantages of composition of matter patent protection for new drug products, from the perspective of the pharmaceutical industry, this protection begins and ends too early. Drug development typically involves the discovery of new compositions long before their value as drugs is established. Patent law promotes early filing of patent applications through novelty and statutory bar standards that put dilatory applicants at risk of losing patent protection entirely.<sup>21</sup> Inventors are well-advised to file patent applications on new compositions of matter as

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17. These acts are defined as infringements in 35 U.S.C. § 271(a).

18. See, e.g., *Allergan v. Alcon Labs.*, 324 F.3d 1322 (Fed. Cir. 2003). For a fuller discussion of this issue, see Rebecca S. Eisenberg, *The Problem of New Uses*, 5 *YALE J. HEALTH POL’Y, L. & ETHICS* 717 (2005).

19. In the examples in the text, the doctors, pharmacists and manufacturers would be liable for actively inducing direct infringements by the patients themselves. 35 U.S.C. § 271(b).

20. There are a number of reasons for this. First, it is more difficult to detect and prove an infringing use than it is to detect and prove an infringing product. Second, it is less efficient to sue numerous users than it is to sue a single manufacturer. Finally, few industries prosper by suing customers. A rare example of an intellectual property owner seeking to enforce its rights by suing customers is the Recording Industry Association of America, which has brought infringement actions against individuals who download copyright-protected music. See Electronic Frontier Foundation, *RIAA v. The People*, <http://www.eff.org/IP/P2P/riaa-v-thepeople.php> (last visited July 24, 2006).

21. A patent application is barred under § 102(b) of the Patent Act if the inventor fails to file within one year of the first publication or other public use of the invention. Moreover, the dilatory applicant who keeps the invention secret risks losing priority to another applicant who subsequently claims the same molecule if the dilatory applicant is deemed to have “abandoned, suppressed, or concealed” the invention. 35 U.S.C. § 102(g).

soon as they can establish patentable utility, typically years before the first commercial marketing of a drug.<sup>22</sup> Under current law,<sup>23</sup> patents expire twenty years after their filing dates, regardless of when they issue.<sup>24</sup> The Hatch-Waxman Act of 1984 provides for patent term extensions of up to five years to compensate for some of the patent life lost during the FDA approval process, so long as the total remaining patent life after extensions does not exceed fourteen years from the date of approval.<sup>25</sup> A study of drugs approved between 1990 and 1995 showed an average “effective patent life” between product launch and patent expiration of 11.7 years, with somewhat longer periods appearing toward the end of the period under study.<sup>26</sup> The effective patent life for a new drug, however, can be far less. For example, the antidepressant drug Paxil did not reach the market until after the original patent had expired.<sup>27</sup>

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22. An invention must be useful in order to be patented. 35 U.S.C. § 101. This requirement may delay the patenting of a new molecule pending discovery of some utility for it. *E.g.*, *Brenner v. Manson*, 383 U.S. 519 (1966) (holding unpatentable a new method of making a new steroid where the steroid had not yet been shown to have a practical utility). But modern cases clarify that the showing of utility necessary to satisfy this requirement of patent law is far less than the showing of safety and efficacy required by the FDA to bring a new drug to market. *E.g.*, *In re Brana*, 51 F.3d 1560, 1567–68 (Fed. Cir. 1995) (“FDA approval . . . is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.”) (citation omitted).

23. The term of U.S. patent protection was changed in 1995 to bring U.S. law into compliance with the Agreement on Trade-Related Aspects of Intellectual Properties (TRIPS).

24. 35 U.S.C. § 154(a)(2). For U.S. patent applications filed prior to 1995, the applicant may instead choose a term that begins when the patent is issued and ends seventeen years later. 35 U.S.C. § 154(c)(1). The seventeen-year term sometimes induced patent applicants to prosecute their claims lethargically in order to defer issuance and prolong the period of patent protection after products got to market. Some patent applicants developed this strategy to a fine art, splitting patent applications into multiple patents and prosecuting them in series to obtain staggered patent terms. Courts, however, have sometimes been skeptical of the validity of the later-issued patents resulting from this strategy. *See, e.g.*, *Geneva Pharm. v. Glaxo SmithKline*, 349 F.3d 1373 (Fed. Cir. 2003) (generic competitor successfully challenged the validity of later-issued patents deriving from the same parent application as expired patents on the antibiotic Augmentin on grounds of “double-patenting”).

25. The period of extension may include half of the time spent in clinical trials before submitting a new drug application (NDA) to the FDA, and all of the time that the NDA is pending before the FDA prior to approval, with provision for adjustment if the applicant did not act with due diligence. 35 U.S.C. § 156(c), (g)(1)(B), (g)(6).

26. Henry G. Grabowski and John M. Vernon, *Effective Patent Life in Pharmaceuticals*, 19 INT'L J. TECH. MGMT. 98 (2000). Subsequent to the study period, Congress provided for additional six-month extensions for pediatric studies in the Food and Drug Administration Modernization Act of 1997.

27. *See SmithKline Beecham v. Apotex Corp.*, 403 F.3d 1331 (Fed. Cir. 2005). The basic patent on the class of compounds that included the molecule that was ultimately brought to market under the brand name Paxil® issued on February 8, 1977 with a terminal disclaimer causing it to expire on October 14, 1992. U.S. Patent No. 4,007,196. A terminal disclaimer is a



Skeptics of the value of regulation may be tempted to blame regulatory lassitude for the long time it takes to bring new drugs to market. But, although regulatory review will never be instantaneous, FDA review times have been greatly reduced since the enactment of the Prescription Drug User Fee Act (PDUFA) in 1992.<sup>28</sup> PDUFA brought the agency new resources to hire additional staff to expedite the review process, and made these new resources contingent upon timely reviews. FDA data from 2003 indicate that almost all NDAs are reviewed within ten months of their submission dates, with median approval times of 7.5 months for priority applications and 12.8 months for standard applications.<sup>29</sup> These periods account for only a small portion of the patent life used up before a new drug gets to market.

A far greater source of delay is simply the time it takes—in the laboratory and in clinical trials—for firms to figure out the effects of patented molecules in patients.<sup>30</sup> This information is an integral part of the value of new drugs, and a patent term that begins long before this

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surrender by the patent applicant of a portion of the patent term, usually to avoid a “double patenting” rejection of a patent that claims an obvious variation on a previously patented invention. The terminal disclaimer causes the second patent to expire on the same date as the first, thereby avoiding an extension of the patent term through patenting essentially the same invention twice. *See In re Longi*, 759 F.2d 887 (Fed. Cir. 1985). Smithkline Beecham (SKB) brought a hemihydrate form of Paxil to market in 1993, following FDA approval of its NDA on December 29, 1992. Historical information on the approval history of Paxil and other drugs is available on the FDA website. CDER New and Generic Drug Approvals: 1998–2004, <http://www.fda.gov/cder/approval/index.htm> (last visited Aug 2, 2004). SKB obtained a separate patent on the hemihydrate form of the molecule, U.S. Patent No. 4,721,723 (issued January 26, 1988), which was still in effect on the FDA approval date, and SKB selected the later patent for term extension. *See* 35 U.S.C. § 156(c)(4) (“in no event shall more than one patent be extended . . . for the same regulatory review period for any product.”). The Federal Circuit ultimately held this patent invalid, reasoning that the earlier patent application on the anhydrate form of the molecule inherently disclosed the hemihydrate form, giving rise to a statutory bar under 35 U.S.C. § 102(b).

Term extensions are unavailable after patents expire, 35 U.S.C. § 156(a)(1), although interim extensions may be obtained if it appears that the regulatory review period will extend beyond the term of the patent. 35 U.S.C. § 156(d)(5).

28. Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, 106 Stat. 4491 (codified as amended at 21 U.S.C. § 379). Congress has extended the user fee program twice, first in the Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 103, 111 Stat. 2296, 2299–304 (1997), and again in the Prescription Drug User Fee Amendments of 2002. Public Health Security and Bioterrorism Preparedness and Response Act of 2002, tit. 5, Pub. L. No. 107-188, §§ 501 et seq. (2002).

29. FDA, OVERVIEW OF PDUFA, available at <http://www.fda.gov/oc/pdufa/report2003/overview2003.html>.

30. Of course, to the extent that regulators require the collection and submission of this information, one might still blame regulation for the time lost in testing the effects of drugs. Whether the value of the information is high enough to justify the delay in product introduction is an important question that is related to, but distinct from, the question explored in the text of whether the patent term as a source of exclusive rights is poorly timed to motivate drug development.

information is generated is poorly timed to allow patent holders to capture the value of these information-dependent products.

In recent years drug innovators have sought to prolong their effective periods of patent protection through various “evergreening” strategies that add new patents to their quivers as old ones expire.<sup>31</sup> Examples include patents on “metabolites” (i.e., the products into which drugs are transformed in a patient’s body);<sup>32</sup> patents on intermediate products used in producing drugs;<sup>33</sup> patents on new uses for drugs;<sup>34</sup> and patents on new formulations or preparations.<sup>35</sup> Some innovating firms have succeeded in getting such patents issued by the PTO, and in using them to defer FDA approval of generic products for years pending resolution of patent infringement claims.<sup>36</sup> The industry’s track record in actually winning these infringement claims, however, has been considerably worse,<sup>37</sup> suggesting that the combination of patents and FDA regulation is doing more to protect these patent holders from competition than the patents could do alone.

Meanwhile, pharmaceutical firms increasingly find themselves targeted with demands to pay for licenses to use the patented inventions of biotechnology firms and universities. Some biotechnology firms try to

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31. See Terry G. Mahn, *Patenting Drug Products: Anticipating Hatch-Waxman Issues During the Claims Drafting Process*, 54 *FOOD & DRUG L.J.* 245, 249–52 (1999); FED. TRADE COMM’N, *GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY* (2002), available at <http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf> [hereinafter *FTC STUDY*].

32. See, e.g., *Schering Corp. v. Geneva Pharm.*, 348 F.3d 992 (Fed. Cir. 2003); *Novartis Pharm. v. Eon Labs Mfg.*, 363 F.3d 1306 (Fed. Cir. 2004).

33. See, e.g., *Ben Venue Labs. v. Novartis Pharm.*, 10 F. Supp. 2d 446 (D.N.J. 1998).

34. See, e.g., *Allergan v. Alcon Labs.*, 324 F.3d 1322 (Fed. Cir. 2003).

35. See, e.g., *Biovail Corp. v. Andrx Pharm.*, 239 F.3d 1297 (Fed. Cir. 2001).

36. See, e.g., *Apotex, Inc. v. Thompson*, 347 F.3d 1335 (Fed. Cir. 2003).

37. See, e.g., *SmithKline Beecham v. Apotex Corp.*, 403 F.3d 1331 (Fed. Cir. 2005) (disclosure of drug in patent application more than a year prior to filing of patent application on metabolite created statutory bar rendering metabolite patent invalid); *Glaxo Wellcome v. Impax Labs.*, 356 F.3d 1348 (Fed. Cir. 2004) (affirming summary judgment of noninfringement of patent on sustained release formulation of bupropion hydrochloride in favor of the generic competitor that used HPC in lieu of HPMC as specified in claim); *Geneva Pharm. v. GlaxoSmithKline*, 349 F.3d 1373 (2003) (holding invalid on grounds of nonstatutory double patenting subsequently issued patents related to the antibiotic on which previously issued patents had expired); *Schering Corp. v. Geneva Pharm.*, 348 F.3d 992 (Fed. Cir. 2003) (expired patent on active ingredient in Claritin™, which issued more than a year before earliest priority date for patent in suit on metabolite, rendered later patent invalid under doctrine of inherent anticipation). In a telling sign of judicial skepticism toward pharmaceutical evergreening patents, in some cases different judges have offered markedly different explanations for why the patent owner should lose, agreeing only on the outcome. Compare *SmithKline Beecham v. Apotex Corp.*, 403 F.3d 1331 (Fed. Cir. 2005) (opinion of Rader, J., holding patent invalid under 35 U.S.C. § 102(b)) with *id.* at 1347 (opinion of Gajarsa, J., holding patent invalid under 35 U.S.C. § 101) and *SmithKline Beecham Corp. v. Apotex Corp.*, 247 F. Supp. 2d 1011 (N.D. Ill. 2003) (opinion of Posner, J., sitting by designation, holding patent valid but not infringed).

stake out market niches “upstream” of drug development, using patents as leverage to get pharmaceutical firms to partner with them to use their proprietary research platforms to develop new products. Universities have also become increasingly aggressive patent holders in the last 25 years, since passage of the Bayh-Dole Act of 1980<sup>38</sup> encouraged them to patent discoveries made with federal funds.<sup>39</sup> A large percentage of university patenting activity is in biomedical research,<sup>40</sup> and universities have not hesitated to enforce their patents against pharmaceutical firms.<sup>41</sup> One way or another, most of these new patent-seekers are pursuing a piece of the action in the profitable business of drug development. They thus contribute to the costs of drug development as well as to its profits.

Patents on *drugs* make drug development profitable by providing patent owners with exclusivity in the market for new pharmaceutical products, but patents on drugs are not the only patents that arise along the road to the pharmaceutical marketplace. Patents cover inventions, and inventions do not necessarily correspond to product markets. Many inventions feed into drug development, including research platform technologies like genomic information and databases, newly identified

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38. Act of Dec. 12, 1980, Pub. L. No. 96-517, § 6(a), 94 Stat. 3015, 3019–28 (1980) (codified as amended at 35 U.S.C. §§ 200–212 (1994)).

39. Universities owned 1.4% of all non-Federally owned U.S. patents issued between 1969 and 1989; by 1999 that number had risen to 4.8%. U.S. PAT. & TRADEMARK OFFICE, U.S. COLLEGES AND UNIVERSITIES—UTILITY PATENT GRANTS 1969–2003, available at [http://www.uspto.gov/web/offices/ac/ido/oeip/taf/univ/asgn/table\\_1.htm](http://www.uspto.gov/web/offices/ac/ido/oeip/taf/univ/asgn/table_1.htm).

40. See David C. Mowery et al., *The Growth of Patenting and Licensing by U.S. Universities: An Assessment of the Effects of the Bayh-Dole Act of 1980*, 30 RES. POL'Y. 99, 117 (2001) (noting that leading patents at the University of California, Stanford, and Columbia “are concentrated in the biomedical area.”); see also Annetine C. Geljins & Samuel O. Thier, *Medical Innovation and Institutional Interdependence: Rethinking University-Industry Connections*, 287 JAMA 72, 75 (2002) (observing that the medical center at Columbia accounts for nearly 85% of the University’s licensed inventions); DAVID C. MOWERY ET AL., *IVORY TOWER AND INDUSTRIAL INNOVATION: UNIVERSITY-INDUSTRY TECHNOLOGY TRANSFER BEFORE AND AFTER THE BAYH-DOLE ACT* (2004).

41. For example, the University of Rochester’s federally-funded research on the Cox-2 enzyme, which plays an important role in the inflammation process, yielded a patent that claimed inhibitors of this enzyme. The university brought patent infringement actions against pharmaceutical companies that made Cox-2 inhibitors, including such once lucrative products as Vioxx (Merck) and Celebrex (Pfizer). See *Univ. of Rochester v. G.D. Searle & Co.*, 249 F. Supp. 2d 216 (W.D.N.Y. 2003), *aff’d*, 358 F.3d 916 (Fed. Cir. 2004), *reh’g & reh’g en banc denied*, 375 F.3d 1303 (Fed. Cir. 2004). The University of California’s \$200 million settlement with Genentech, M. Barinaga, *Genentech, UC Settle Suit for \$200 Million*, 286 SCIENCE 1655 (1999), and the University of Minnesota’s \$300 million settlement with Glaxo-Wellcome, *The U Has Settled a Year Old Lawsuit*, 29 UNIV. OF MINN. BRIEF, Oct. 13, 1999, available at <http://www1.umn.edu/urelate/brief/1999-10-13.html>, have emboldened others to follow with their own lawsuits, including Baylor College of Medicine, Cornell University, Columbia University, University of Rochester and the Massachusetts Institute of Technology. See Margaret C. Fisk, *Ivory Towers Fire Back Over Patents: More Schools Are Suing Businesses*, NAT’L LAW J., Aug. 26, 2002, at A1.

(or characterized) drug targets, genetically engineered animal models, and new laboratory techniques, instruments, and reagents. These “upstream” inventions, which help to explain disease pathways and mechanisms and to identify potential targets for therapeutic interventions, are increasingly likely to be patented, and patents on these numerous discoveries impose costs on drug development.<sup>42</sup> From the perspective of a drug-developing firm, these new patents are so many siphons at the feeding trough of the next pharmaceutical blockbuster, draining away profits in many different directions.

In sum, although the party line of the pharmaceutical industry continues to endorse strong patent protection throughout the world, firms must recognize that the patent system has become a mixed blessing for their bottom lines, adding to costs as well as profits. Moreover, as the science of drug development becomes more complex, as time to market from discovery of a new molecule grows longer and more uncertain, and as the courts grow more skeptical of evergreening strategies, patents can not always be counted upon to secure effective market exclusivity for drug developing firms beyond that provided by the FDA.

## II. FDA REGULATION: PROFITS AS WELL AS COSTS

FDA regulation does much to support the profitability of drug development even as it adds to its costs. Like other costly regulatory regimes, FDA regulation serves as a barrier to entry that protects market incumbents from competition from new firms. The size of this particular entry barrier is not merely an inadvertent artifact of regulations that aim to protect health and safety. Instead, it has been carefully calibrated in legislative compromises that balance the interests of pioneering drug developers against those of consumers and generic competitors.

The most important of these legislative compromises is the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the “Hatch-Waxman Act.”<sup>43</sup> Prior to passage of the Hatch-Waxman Act, the hurdle of FDA approval was high enough to keep generic equivalents of most drugs off the market long after the drugs went

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42. Rebecca S. Eisenberg, *Bargaining Over the Transfer of Proprietary Research Tools: Is This Market Failing or Emerging?*, in EXPANDING THE BOUNDARIES OF INTELLECTUAL PROPERTY: INNOVATION POLICY FOR THE KNOWLEDGE SOCIETY (R. Dreyfuss et al. eds., 2001).

43. Act of Sept. 24, 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended at 15 U.S.C. §§ 68b–68c, 70b; 21 U.S.C. §§ 301, 355, 360cc; 28 U.S.C. § 2201; and 35 U.S.C. §§ 155, 155A, 156, 271, and 282). See Alfred B. Engelberg, *Special Patent Provisions for Pharmaceuticals: Have They Outlived Their Usefulness? A Political, Legislative and Legal History of U.S. Law and Observations for the Future*, 39 IDEA 389 (1999).

off patent. The FDA took the position that generic versions of previously approved drugs were themselves “new drugs” requiring proof of safety and efficacy before they could be brought to market.<sup>44</sup> At the same time, the FDA treated clinical trial data submitted to the agency by pioneer firms as proprietary information belonging to the submitter, which the agency would not disclose or permit others to rely upon in their applications.<sup>45</sup> Moreover, generic drug companies could not conduct their own clinical trials until after patents on the drugs expired without exposing themselves to infringement liability.<sup>46</sup> Even after patent expiration, generic firms faced prohibitive regulatory costs that they could not recoup in the low-margin, competitive market for off-patent drugs. Generic firms argued that the regulatory entry barrier had to be lowered for generic products in order to bring about price competition in the market for off-patent drugs.<sup>47</sup> Manufacturers of pioneer drugs argued that it was only fair that FDA regulation of generic products should delay generic entry beyond patent expiration, since FDA regulation typically consumed years of the patent terms for pioneer drugs.<sup>48</sup>

Congress responded to these competing criticisms of the status quo with a package of measures that blurred the functional distinction between drug regulation and patents. For generic manufacturers, the Hatch-Waxman Act provided a streamlined process for obtaining FDA approval to sell a product that is “bioequivalent” to a previously approved product through use of an abbreviated new drug application (ANDA),<sup>49</sup> and permitted the necessary clinical trials to proceed during the patent term without infringement liability.<sup>50</sup> For research pharmaceutical firms, the Hatch-Waxman Act directed PTO to grant patent term extensions of up to five years to compensate for marketing delays during the regulatory

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44. Response to Petition Seeking Withdrawal of the Policy Described in the Agency’s “Paper” NDA Memorandum of July 31, 1978, 45 Fed. Reg. 82052 (Dec. 12, 1980). See generally Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1792–93 (1996) and sources cited therein. A limited exception permitted the introduction of generic versions of products that had been on the market since before 1962 on the basis of abbreviated applications.

45. Public Information, 39 Fed. Reg. 44,602 (Dec. 24, 1974).

46. Roche Prods. v. Bolar Pharm., 733 F.2d 858 (Fed. Cir. 1984).

47. Generic versions of previously approved products were sometimes approved on the basis of “paper NDAs,” which relied upon published data concerning the safety and efficacy of the previously approved drug to obtain approval for a bioequivalent product, but such data were not always available. See Engelberg, *supra* note 43, at 396–97. The Hatch-Waxman Act authorized continued use of paper NDAs in a provision codified at 21 U.S.C. § 355(b)(2).

48. For a history of the Hatch-Waxman Act from the perspective of the Pharmaceutical Manufacturers Association, see Ellen J. Flannery & Peter Barton Hutt, *Balancing Competition and Patent Protection in the Drug Industry: The Drug Price Competition and Patent Term Restoration Act of 1984*, 40 FOOD DRUG COSM. L.J. 269 (1985).

49. Federal Food, Drug, and Cosmetic Act § 505(j); 21 U.S.C. § 355(j).

50. 35 U.S.C. § 271(e).

review period prior to the first permitted commercial marketing of a new drug.<sup>51</sup> At the same time, it set up a complex system for keeping track of patents that cover FDA-approved drugs and directed the FDA to defer regulatory approval of generic versions of those drugs until after patent expiration.<sup>52</sup> In this system, competing manufacturers who believe that their products do not infringe these patents, or that the patents are invalid, can file ANDAs prior to patent expiration. If the patent owner files an infringement action within 45 days, however, FDA approval of the ANDA is stayed for 30 months. This stay takes effect regardless of the underlying merits of the legal arguments (except in the unlikely event that a court resolves the issue sooner).<sup>53</sup> In effect, this 30-month stay of regulatory approval is like a preliminary injunction in favor of a patent holder, administered by FDA rather than by a trial court, and with no requirement to show likelihood of success on the merits.<sup>54</sup>

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51. 35 U.S.C. § 156. *See supra* note 25.

52. 21 U.S.C. § 355(b), (c), (j).

53. Holders of approved new drug applications (NDAs) are required to disclose all patents that they believe would be infringed by unauthorized sales of the approved drug, and the FDA publishes the list in a publication called the Orange Book. Firms soon recognized that it made sense for them to list expansively any relevant patents, including, for example, patents covering aspects of the product formulation that are easy to design around to avoid infringement. Such an expansive approach preserved opportunities to file multiple lawsuits that triggered multiple 30-month stays of FDA approval, in effect, prolonging the period of profitable market exclusivity beyond what the listed patents (which could be invalid or not infringed, or at least not so clearly valid and infringed as to justify a preliminary injunction) could do on their own. *See* FTC STUDY, *supra* note 31. For a particularly egregious example of this strategy, see *Apotex, Inc. v. Thompson*, 347 F.3d 1335 (Fed. Cir. 2003) (holding that Hatch-Waxman Act does not require the FDA to review patents for validity and infringement before listing them).

54. In 2002, the Bush administration announced a plan to limit patent holders to a single 30-month stay per product by FDA rule. *See* FDA, Application for FDA Approval to Market a New Drug: Patent Listing Requirements and Application of 30-month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed (proposed Sept. 19, 2002) (to be codified at 21 C.F.R. pt. 314), <http://www.fda.gov/OHRMS/DOCKETS/98fr/PATENT.pdf> [hereinafter "Patent Listing Requirements"]. The FTC had previously proposed such a rule. FTC STUDY, *supra* note 31, at ii. According to the Congressional testimony of Lester Crawford, then Deputy Commissioner of Food and Drugs, 17 out of 442 active ANDAs that involve patent challenges have had multiple 30-month stays, including a significant number of products with high dollar value annual sales. *Hearing Before the Subcomm. on Health, H.R. Comm. on Energy & Commerce*, 107th Cong. (2002) (statement of Lester M. Crawford, Deputy Comm'r of Food and Drugs), *available at* [http://www.fda.gov/ola/2002/hatch\\_waxman1009.html](http://www.fda.gov/ola/2002/hatch_waxman1009.html). The final rule is set forth at 68 Fed. Reg. 36676 (June 18, 2003).

Somewhat different limitations on the availability of 30-month stays were codified as part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003. Pub. L. No. 108-173 § 1101, 117 Stat. 2066, 2448 (codified as amended at 21 U.S.C. § 355(j)). That act provides that for ANDAs filed after August 18, 2003, a 30-month stay is available only for litigation involving patents submitted to the FDA prior to the date that the ANDA was submitted. *Id.* § 1101(a)(2)(A)(ii)(I), (b)(2)(B)(i) (codified at 21 U.S.C. § 355(j)(5)(B)(iii), (c)(3)(C)).

In this new regime, it is difficult to tell just how much work is being done by patents and how much by drug regulation in deferring generic entry. Congress has sought to synchronize and calibrate the entry barriers posed by the two legal regimes. The FDA is pervasively called upon to track patents in administering its system of drug approvals, although without ever making substantive judgments about patent validity and infringement. At the same time, the PTO is called upon to track the FDA approval process in timing the expiration of patents. The two systems operate in tandem to confer exclusivity in markets for new products and to determine when that exclusivity should end, blurring the line between concerns about health and safety and efforts to reward innovation.

### III. FDA-ADMINISTERED PSEUDO-PATENTS

Other legislative initiatives have cast the FDA in the role of administering pharmaceutical pseudo-patents, unabashedly directing the FDA to use its market gatekeeper role to provide firms with market exclusivity in exchange for investing in certain kinds of pharmaceutical R&D. An early example of this is the Orphan Drug Act of 1983,<sup>55</sup> which directs the agency to grant seven years of market exclusivity for products to treat rare diseases and conditions affecting fewer than 200,000 patients in the United States.<sup>56</sup> Although one might expect that products qualifying for this protection would have markets too small to be lucrative, in fact, many products qualifying for exclusivity under the Orphan Drug Act have had large and profitable markets for off-label use.<sup>57</sup> The effect of FDA-administered market exclusivity under the Orphan Drug Act is similar to the effect of a patent on a particular use of a drug.<sup>58</sup>

In 1984 Congress added two more provisions for FDA-administered market exclusivity in the Hatch-Waxman Act, providing five years of market exclusivity for new chemical entities not previously approved by

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55. Pub. L. No. 97-414, 96 Stat. 2049.

56. Under § 527 of the Federal Food, Drug, and Cosmetic Act, if the FDA approves a new drug application for a drug that it has designated for a rare disease or condition, “the Secretary may not approve another application . . . for such drug for such disease or condition for a person who is not the holder of such approved application . . . until the expiration of seven years from the date of the approval of the approved application . . . .” 21 U.S.C. § 360cc(a).

57. “Off-label” use of a drug means use for a purpose other than that for which the FDA has approved the drug as safe and effective.

58. The exclusivity conferred by the Orphan Drug Act is limited to a prohibition against approval of another application “for such drug for such disease or condition,” and thus does not preclude approval of either (1) another drug for the same disease or condition, or (2) the same drug for another disease or condition. *Genentech, Inc. v. Bowen*, 676 F. Supp. 301 (D.D.C. 1987); *Sigma-Tau Pharms. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002).

the FDA,<sup>59</sup> and three years of exclusivity for making changes in a previously approved product that required conducting new clinical trials to win FDA approval.<sup>60</sup> In contrast to the Orphan Drug Act provisions, these Hatch-Waxman Act exclusivity provisions merely prevent the FDA from allowing competitors to obtain a streamlined review of their applications without having to submit a full NDA. They do not prevent a competitor from obtaining approval if it is willing to go to the trouble and expense of conducting its own clinical trials and to rely strictly on its own data for proof of safety and efficacy. In effect, these provisions amount to FDA-administered proprietary rights in regulatory data, awarded to encourage particular kinds of innovation in drug development rather than to protect consumers from unsafe or ineffective drugs. The practical effect is to defer generic competition, even without patent protection.

The five-year period of data exclusivity for a new chemical entity begins with first market approval and therefore often runs concurrently with patent protection, although in some cases it may last longer.<sup>61</sup> The three-year period of data exclusivity for making product changes that require clinical trials to gain approval begins with the approval of the supplemental application, making it more amenable to strategic manipulation to prolong market exclusivity. For example, as a product approaches the end of its patent life, a firm might seek approval to switch the product from prescription to over-the-counter sales, after testing the product in patients to determine if they may safely self-administer it without the supervision of a physician.<sup>62</sup> The data exclusivity thereby gained is limited to the terms of the new approval, and will not prevent a competitor from using an ANDA to sell the product as previously approved, or for previously approved indications.

This has proven to be a very significant limitation on the use of a supplemental NDA to gain approval to market a drug for a new indication.<sup>63</sup> The three-year exclusivity does not preclude a generic competitor from getting approval to sell its version of the product for the original indication, and once the generic version is available on the market, the FDA can do nothing to stop physicians from prescribing the generic

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59. 21 U.S.C. § 355(j)(5)(F)(ii).

60. 21 U.S.C. § 355(j)(5)(F)(iii). This latter source of exclusivity might be available, for example, to a manufacturer that makes a change in the dosage form for a product, or that seeks approval of a drug for a new indication, or conducts clinical trials to determine whether a drug may safely be switched from prescription to over-the-counter (OTC) status.

61. See *supra* note 9 and accompanying text (discussing Paxil).

62. The strategic considerations behind the timing of these moves are laid bare in studies by consulting firms that are posted on the internet. See, e.g., Kline & Co., *Impending Wave of Rx-to-OTC Switches Offers Significant Opportunities for Drug Companies*, Aug. 15, 2002, [http://www.klinegroup.com/news/6\\_2002815.asp](http://www.klinegroup.com/news/6_2002815.asp).

63. *Bristol-Myers Squibb v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996).



product off-label for the new indication. Indeed, unless the new indication involves a different formulation of the product, state generic substitution laws may pressure the original innovator to lower its prices to avoid generic substitution at the point of filling the prescription.<sup>64</sup>

The Food and Drug Administration Modernization Act of 1997 added a provision for six months of exclusivity as a reward for conducting pediatric trials of drugs.<sup>65</sup> This six-month period of exclusivity is not contingent upon approval of the drug as safe and effective in children and is not limited to pediatric use of the drug. It simply extends any existing market exclusivity held by the submitter, whether under a patent, the Orphan Drug Act, or Hatch-Waxman exclusivity provisions,<sup>66</sup> further deferring the time when FDA might approve a competing generic product.

Each of these provisions confers patent-like protection under the auspices of the FDA rather than the PTO. Although the resulting protection is often linked to submission and consideration of data from clinical trials of drugs for safety and efficacy, each of these exclusivity provisions may be better understood as an economic measure designed to promote costly investments in innovation than as a consumer protection measure designed to keep unsafe or ineffective products off the market. In each case, FDA regulation serves a function traditionally relegated to the patent system: promoting and rewarding investments in innovation by granting valuable exclusionary rights.<sup>67</sup>

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64. See Henry G. Grabowski & John M. Vernon, *Substitution Laws and Innovation in the Pharmaceutical Industry*, 43 J.L. & CONTEMP. PROBS. 43, 49–56 (1979).

65. Pub. L. No. 105-115, 111 Stat. 2296. Although this provision was originally set to expire after five years, it has been extended. See Best Pharmaceuticals for Children Act of 2002, P.L. 107-109, 115 Stat. 1408 (codified as amended in scattered provisions of Titles 21 and 42 of U.S.C.).

66. See 28 U.S.C. § 355a.

67. Another controversial Hatch-Waxman Act provision that has the effect of using the FDA to prolong the period of exclusivity in product markets is the provision of a 180-day period of exclusivity to the first generic applicant to file a patent challenge against any approved drug. 21 U.S.C. § 355(j)(5)(B)(iv); see FTC STUDY, *supra* note 31, at 57–63. Designed to spur generic competition with products covered by questionable patents, the provision had the unintended effect of providing a strategic opportunity to defer generic competition in products that patent law would otherwise leave unprotected. The first challenger and the patent owner would reach a litigation settlement that affirmed the validity and infringement of the questionable patent, deferring the effective date of any subsequently filed ANDA for the same drug indefinitely while rendering subsequent challengers ineligible for the 180-day exclusivity. The FTC challenged this strategy under the antitrust laws, *id.* at 1–2, and Congress moved to curtail these strategies as part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 by defining certain “forfeiture events” that would cause the first generic applicant to lose its right to generic exclusivity. Pub. L. No. 108-173 § 1102, 117 Stat. 2066, 2458 (codified in pertinent part at 21 U.S.C. § 355(j)(5)(D)). But insofar as this exclusivity is still available, it is another example of how the combination of patents and drug-specific regulation provides longer exclusivity than the patent system could do on its own.

Another important role played by the FDA in supplementing the exclusivity provided by patents is protecting patent holders against parallel imports of drugs previously sold at a lower price in another country. Since drugs are more expensive in the United States than anywhere else in the world,<sup>68</sup> the profits from sales in the United States are potentially vulnerable to erosion through arbitrage that moves drugs from low-price (foreign) to high-price (domestic) markets.<sup>69</sup>

The legal status of this arbitrage under the patent laws is not entirely clear. Under the “first sale” doctrine, the sale of a patented article by or with the permission of the owner exhausts the patent monopoly with respect to that article.<sup>70</sup> This doctrine plainly permits buyers to resell in the U.S. secondary market any goods (such as used cars) that were purchased in the United States without having to get renewed permission from the owners of the patents on the goods and their various components. It is less clear whether it permits importers of patented drugs from Canada, for example, to resell them in the United States.

This is a point on which the national patent laws of different countries are in disagreement. Some countries follow a rule of “national exhaustion,” which means that the first sale doctrine only permits resales within the same country, while others follow a rule of “international exhaustion,” which means that once the patent holder has authorized sale of a patented article anywhere in the world, the purchaser is free to resell it anywhere without needing further permission. This issue has generated considerable debate in trade negotiations, but so far there has been no agreement and each nation is free to choose its own exhaustion rule.<sup>71</sup>

The U.S. bargaining position in trade negotiations, supported by the pharmaceutical industry, has favored imposition by treaty of a uniform rule of national exhaustion.<sup>72</sup> But it is not entirely clear that this is currently the law in the United States.<sup>73</sup> The U.S. Court of Appeals for the

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68. See Judith L. Wagner & Elizabeth McCarthy, *International Differences in Drug Prices*, 25 ANN. REV. PUB. HEALTH 475 (2004).

69. See Claude E. Barfield & Mark A. Groombridge, *Parallel Trade in the Pharmaceutical Industry: Implications for Innovation, Consumer Welfare, and Health Policy*, 10 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 185 (1999).

70. See *Intel Corp. v. ULSI Sys. Tech.*, 995 F.2d 1566 (Fed. Cir. 1993).

71. Agreement on Trade Related Aspects of Intellectual Property Rights, art. 5, sec. 1(a), art. 6, April 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, Legal Instruments-Results of the Uruguay Round vol. 31, 33 I.L.M. 81 (1994), available at [http://www.wto.org/english/tratop\\_e/trips\\_e/t\\_agm0\\_e.htm](http://www.wto.org/english/tratop_e/trips_e/t_agm0_e.htm) [hereinafter “TRIPS Agreement”].

72. DANIEL GERVAIS, *THE TRIPS AGREEMENT: DRAFTING HISTORY AND ANALYSIS* 112–15 (2d ed. 2005).

73. For a careful analysis of this question prior to the Federal Circuit’s decision in *Jazz Photo Corp. v. International Trade Commission*, 264 F.3d 1094 (Fed. Cir. 2001), see Margreth

Federal Circuit once observed in passing, with no acknowledgment of controversy, that under U.S. patent law the first sale doctrine only applies if there has been a sale in the United States.<sup>74</sup> But the U.S. Supreme Court has arguably held otherwise in the copyright context, at least if the goods were manufactured in the United States,<sup>75</sup> and in the trademark context, at least if the goods come from a company that is owned by or affiliated with the U.S. mark owner.<sup>76</sup>

Despite the uncertain coverage of U.S. patent law, FDA regulation protects patent owners against parallel imports of drugs. This protection arises in part from differences in labeling requirements for drugs sold in different markets.<sup>77</sup> But the pharmaceutical industry does not rely on these regulatory differences to protect it from parallel trade in drugs in the United States. Congress fortified protection against parallel imports by enacting the Prescription Drug Marketing Act of 1987, which specifically prohibits reimportation of previously exported U.S.-manufactured drugs except by the manufacturer, unless required for emergency medical care.<sup>78</sup> There is a genuine health and safety issue lurking behind these provisions,<sup>79</sup> but they also have an economic side effect that may be even more important—preserving the viability of price discrimination across national markets for drugs. This economic side effect has brought renewed political attention to the prohibition against reimportation, as legislators, insurers, and entrepreneurs have sought to give U.S. consumers the benefit of cheaper drug prices in Canada and other countries.<sup>80</sup>

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Barrett, *The United States' Doctrine of Exhaustion: Parallel Imports of Patented Goods*, 27 N. KY. L. REV. 911 (2000).

74. *Jazz Photo*, 264 F.3d 1094 (“United States patent rights are not exhausted by products of foreign provenance. To invoke the protection of the first sale doctrine, the authorized first sale must have occurred under the United States patent.”).

75. *Quality King Distribs. v. Lanza Research Int'l*, 523 U.S. 135 (1998).

76. *KMart Corp. v. Cartier, Inc.*, 486 U.S. 281 (1988).

77. FDA approval to market a new drug is contingent upon the inclusion of specified information in the accompanying label about indications, dosage, side effects, etc. In an interesting counterpoint to the push toward harmonization of national regulations to promote free trade, the most enduring obstacle to parallel trade in drugs may prove to be national differences in drug regulation that make products manufactured for one market difficult to sell elsewhere. In this respect, differences in national laws operate to the advantage of the pharmaceutical industry, while harmonization efforts loom as a long-term threat to profits.

78. Pub. L. No. 100-293, 102 Stat. 95 (codified as amended at 21 U.S.C. §§ 301, 331, 333, 353, 381, & 801(d)).

79. See Press Release, FDA, FDA/U.S. Customs Import Blitz Exams Reveal Hundreds of Potentially Dangerous Imported Drug Shipments (Sept. 29, 2003), <http://www.fda.gov/bbs/topics/NEWS/2003/NEW00948.html>.

80. See, e.g., *Vermont v. Leavitt*, 405 F. Supp. 2d 466 (D. Vt. 2005). The ultimate political resolution of this issue remains uncertain. See Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, §§ 1121–23, 117 Stat. 2066, 2464. For a libertarian argument that markets should be permitted to equalize the prices charged for drugs in

Meanwhile, the federal government, invoking health and safety concerns, has taken the lead in prosecuting reimporters of drugs from Canada,<sup>81</sup> thereby relieving pharmaceutical firms of the burden of enforcing their own economic interests against defendants who present themselves as champions of access to affordable drugs.

In sum, FDA regulation is an important source of protection for drug-developing firms against competition from free riders and thereby enhances the profitability of drug development. This protection is in part a side effect of regulatory moves that can be justified entirely in terms of protecting health and safety. But at times it is more overtly about motivating firms to invest in particular types of R&D, such as developing orphan drugs, bringing new chemical entities to market, and conducting further clinical trials of previously approved products.

#### IV. FDA PSEUDO-PATENTS VS. PATENTS

To the extent that legal regulation deliberately provides protection against competition in product markets as an economic incentive for R&D, one might ask whether it makes sense to provide such protection through FDA-administered rules rather than through patent law. Economic incentives for R&D are traditionally the province of the patent system, and arguably outside the core competence of the FDA in protecting public health.<sup>82</sup> Nonetheless, there are advantages to using FDA regulation as a mechanism for providing product exclusivity.

The patent system is a one-size-fits-all legal regime that applies essentially the same rules to inventions arising in biopharmaceutical research, automotive engineering, information technology, semiconductors, rocket science, and even business methods. But the needs of these fields for patent protection differ greatly, making it difficult to fine-tune the patent laws to meet the needs of the pharmaceutical industry without upsetting the balance of protection and competition in other industries. U.S. patent law has some industry-specific provisions, including the Hatch-Waxman patent term extension provisions,<sup>83</sup> biotechnology proc-

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different countries, *see* Roger Pilon, *Drug Reimportation: The Free Market Solution*, 2004 CATO INST. POL'Y ANALYSIS NO. 521, available at <http://www.cato.org/pubs/pas/pa521.pdf>.

81. *See, e.g.*, *United States v. Rx Depot, Inc.*, 290 F. Supp. 2d 1238 (N.D. Okla. 2003).

82. The unease of the FDA in this relatively new role is perhaps reflected in its reluctance to evaluate whether the patents designated by pharmaceutical firms for listing in the Orange Book are appropriately listed or not, and in its reluctance to consider whether there is any plausible basis for asserting that a generic product will infringe such patents before entering a 30-month stay of regulatory approval for the generic product. *See* Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. 50338, 50345 (Oct. 3, 1994) (codified at 21 C.F.R. pt. 314).

83. 35 U.S.C. § 156.

ess patent provisions,<sup>84</sup> and prior user rights for business method patents.<sup>85</sup> Often the result of legislative compromise after a change proposed by one industry meets opposition from another, these provisions are awkward, cumbersome, and are more likely to address the interests of well-heeled rent-seekers than to preserve the public interest.

Industry-specific patent provisions may also place the United States in violation of the TRIPS agreement, which requires signatories to provide patent protection “without discrimination as to the place of invention, *the field of technology* and whether products are imported or locally produced.”<sup>86</sup> The prohibition on discrimination in patent protection by field of technology was much favored by the pharmaceutical industry in the course of trade negotiations in order to force member states to eliminate provisions in their national laws that previously weakened drug patents (such as compulsory licensing provisions).<sup>87</sup> But the treaty language is written in broader terms that seem also to prohibit discrimination in favor of drug patents as well as against them.

FDA-administered exclusivity may be a way around these legal and political problems. To the extent that the exclusivity needs of the pharmaceutical industry are different from those of other industries, it might be less problematic to fine tune the drug regulation rules than it is to fine tune the patent system. If it is too obvious that this is what is really going on, the WTO might decide—perhaps in response to a complaint from a nation with an aggrieved generic drug industry such as India or Israel—that so-called FDA exclusivity is really a patent by another name, and that industry-specific pseudo-patents violate treaty obligations regardless of where the exclusionary rights are located in the U.S. Code. Still, it might be easier to finesse the issue if the protection arises through drug regulation, particularly if the underlying legislation serves a significant interest other than intellectual property, such as the protection of health and safety.

Apart from legal and political constraints on fortifying patent protection for biopharmaceutical inventions, there are at least two reasons why the pharmaceutical industry might prefer FDA-administered exclusivity to stronger patent protection.

First, the FDA provides product market exclusivity while the patent system provides invention exclusivity. Because many inventions are used in the course of product development, strengthening patent protection is

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84. 35 U.S.C. § 103(b).

85. 35 U.S.C. § 273.

86. TRIPS Agreement, *supra* note 71, at art. 27 (emphasis added).

87. See Robert Weissman, *A Long, Strange Trips: The Pharmaceutical Industry Drive to Harmonize Global Intellectual Property Rules, and the Remaining WTO Legal Alternatives Available to Third World Countries*, 17 U. PA. J. INT'L ECON. L. 1069 (1996).

a double-edged sword for innovating firms. While it fortifies the drug patents that provide product market exclusivity, it also fortifies the patents on the many proprietary inputs into drug development, thus adding to the costs as well as the revenues for drug-developing firms. FDA-administered exclusivities, by contrast, enhance product revenues without increasing these costs. Second, FDA-administered exclusivities typically run while a product is on the market, while much or all of a patent term may run earlier than that. As a result, it may be easier for firms to time the period of FDA-administered exclusivity strategically so as to maximize profits.

On the other hand, the relative ease of changing the rules governing FDA-administered exclusivities makes them more vulnerable than patents to legislative and administrative change in response to shifting political currents. In a political environment that reflects more concern about controlling the rising costs of drugs than about fortifying incentives for new drug development, it may be harder for drug-developing firms to sustain FDA-administered measures that currently support high drug prices than it is to sustain the rights conferred by the patent system.<sup>88</sup>

It is politically and legally difficult to change the patent system, particularly in the post-TRIPS era, but there are many levers to push in the drug regulation system to chip away at the market exclusivity that supports current drug prices. Entry barriers achieved through FDA regulation might thus prove less durable than those conferred by patents.

## V. FDA CONTROL OF CLINICAL TRIALS AS INNOVATION POLICY

More central to the health and safety mission of the FDA than the various provisions for securing market exclusivity to drug developers are (1) its role in approving (or disapproving) the marketing of new drugs<sup>89</sup> based on clinical evidence of safety and efficacy<sup>90</sup> and (2) its role in limiting promotional claims that manufacturers make about products under

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88. For example, even the Bush administration, which has enjoyed strong support from the pharmaceutical industry and has been generally quite receptive to its interests, bowed to political pressure to facilitate generic entry by changing FDA rules to limit the kinds of patents that qualify for the prolonged exclusivity benefits of the Hatch-Waxman Act and to permit patent holders only one automatic 30-month stay of generic approval per product pending the resolution of infringement litigation. *See* Patent Listing Requirements, *supra* note 54. This change in policy was initially a result of executive action alone, without the need for new legislation, although Congress promptly followed by codifying similar restrictions as part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003. Pub. L. No. 108-173 § 1101, 117 Stat. 2066, 2448–57 (codified at 21 U.S.C. § 355(j)).

89. Federal Food, Drug, and Cosmetic Act § 505(a).

90. *Id.* § 505(b).

its authority to protect the public from products that are “misbranded.”<sup>91</sup> In performing these core functions, the FDA seems to be protecting patients rather than rewarding innovation, thereby adding to the costs of drug development and limiting its rewards. Yet even in these core roles, the agency’s original function of protecting the public from snake oil has become pervasively intertwined with its more modern function of getting firms to conduct rigorous clinical trials of drugs.<sup>92</sup>

Popular perceptions of the value of these regulatory roles have shifted over time. For much of the history of the FDA, Congress and the courts were broadly supportive of the agency’s conservative stance toward protecting the public from products that might be hazardous, useless, or both. In the past quarter century, attitudes toward the FDA have become more mixed. Today, rather than getting praised as a cautious steward of public health, the FDA is often criticized as a paternalistic bureaucracy interposing costly barriers between patients who demand new products and firms that are eager to supply them.<sup>93</sup> In this changed political environment, the traditional role of the FDA is being reappraised, making it especially important to understand what work FDA regulation actually does.

Justifications for the FDA’s roles that focus on protecting patients from harm invite the objection that patients may be harmed by disease as well as by drugs. Such justifications have become less persuasive as patient advocacy groups and drug developing firms have forged political alliances to streamline the regulatory process. In the early days of the AIDS epidemic many patients argued forcefully that they would rather take the risks posed by investigational drugs that did not have FDA

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91. *Id.* §§ 301, 502.

92. Both functions are apparent in the current statutory language, which retains the indignant early 20th century vocabulary of prior legislative enactments to characterize products that do not meet the standards (“adulterated” and “misbranded”) while using the technocratic vernacular of scientific peer review to characterize the standards themselves (“adequate and well-controlled investigations . . . by experts qualified by scientific training and experience”). More specifically, Section 505(d) provides that the Agency may refuse to approve an application if the investigations that the sponsor submits “do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions in the proposed labeling,” or if there is a lack of “substantial evidence” that the drug will have the effect it purports or is represented to have under the conditions of the proposed labeling, defining “substantial evidence” as “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to . . . .” *Id.* § 505(d).

93. *See, e.g.,* Abigail Alliance v. Von Eschenbach, 445 F.3d 470 (D.C. Cir. 2006) (holding that denying terminally ill patients access to “potentially life-saving medication” not yet approved by the FDA for use outside clinical trials impinges upon an interest protected by due process), *vacated*, 469 F.3d 129 (D.C. Cir. 2006).

approval than allow their illnesses to progress pending the results of definitive clinical trials.<sup>94</sup> It is difficult to make the case for imposing costly and time-consuming regulation as a way of protecting terminally ill patients from risks that they are eager (and impatient) to encounter.

The harshness of withholding potentially life-saving drugs from terminally ill patients clearly troubled the panel majority in the recent decision of the U.S. Court of Appeals for the District of Columbia in *Abigail Alliance v. Von Eschenbach*.<sup>95</sup> The Abigail Alliance, a patient advocacy group, sought access on behalf of terminally ill patients to investigational new drugs that had performed well in preliminary “Phase I” trials in a small number of patients and were therefore approved for testing in “Phase II” trials in a larger group of patients. The court held that the FDA’s policy of denying such access impinged upon substantive due process rights to privacy, liberty and life, suggesting that the FDA was equivalent to a common law tortfeasor who was interfering with efforts to rescue an injured person:

A right of control over one’s body has deep roots in the common law. . . . As recognized throughout Anglo-American history and law, when a person is faced with death, necessity often warrants extraordinary measures not otherwise justified. Indeed, the principle holds even when that action impinges upon the rights of others. . . . Barring a terminally ill patient from the use of a potentially life-saving treatment impinges on this right of self-preservation.

Such a bar also puts the FDA in the position of interfering with efforts that could save a terminally ill patient’s life. Although the common law imposes no general duty to rescue or to preserve a life, it does create liability for interfering with such efforts.<sup>96</sup>

The court remanded the case to the trial court to determine whether the FDA’s policy is narrowly tailored to serve a compelling governmental interest.

The FDA’s protective approach toward the risks posed by drugs seems anomalous when patients enjoy relatively unfettered access to potentially lethal dietary supplements.<sup>97</sup> From a consumer protection

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94. See STEVEN EPSTEIN, *IMPURE SCIENCE: AIDS, ACTIVISM, AND THE POLITICS OF KNOWLEDGE* (1996).

95. 445 F.3d 470, *vacated*, 469 F.3d 129 (D.C. Cir. 2006).

96. *Id.* at 480 (citations omitted).

97. In the case of dietary supplements, such as ephedra, the burden of proof is on the FDA to establish that the product poses an unreasonable risk before it may be removed from the market. 21 U.S.C. § 342(f)(1). After years of regulatory maneuvering, the FDA banned the sale of ephedrine alkaloids after declaring that such products are “adulterated” and present an



perspective, it is difficult to make sense of a two-tiered regulatory system that subjects ethical pharmaceutical products to rigorous scientific standards for proof of safety and efficacy before they reach the market, while allowing substantially untested and unregulated dietary supplements, which purport to have similar effects and pose unknown hazards, to stay on the market until the FDA establishes that they are unreasonably dangerous.

Of course, one might argue that the way to correct the asymmetry is to eliminate the exemptions that currently allow untested dietary supplements and nutraceuticals to remain on the market. But plainly some consumers (including some members of Congress) want these products and do not want the FDA to regulate them, and the consumers and manufacturers of these products have so far succeeded in persuading Congress to keep the FDA off their backs.<sup>98</sup> The existence of a relatively unregulated dietary supplement market alongside a highly regulated pharmaceuticals market nonetheless poses a challenge to a justification for regulation that rests solely on safety and consumer protection. Why keep drugs off the market until their manufacturers prove that they are safe and effective, while allowing dietary supplements to stay on the market until regulators prove that they are unreasonably dangerous?

Another anomalous aspect of the current regulatory regime from a pure consumer protection perspective is the approach to off-label use of products that the FDA has approved for only a narrow set of adequately tested indications. Once the FDA has approved a product for a single indication in a particular group of patients, physicians are free to prescribe it for any patient and for any indication, notwithstanding the absence of any clinical trial data to establish the safety and efficacy of the drug beyond the approved use.<sup>99</sup> Off-label prescription of drugs is a

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unreasonable risk of illness or injury. Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk, 69 Fed. Reg. 6787 (Feb. 11, 2004) (codified at 21 C.F.R. pt. 119). Manufacturers have unsuccessfully challenged this regulation in the courts. *Nutraceutical Corp. v. Crawford*, 459 F.3d 1033 (10th Cir. 2006); *NVE, Inc. v. Dep't of Health & Human Servs.*, 436 F.3d 182 (3d Cir. 2006) (holding that the FDA's factual and legal determinations in its rule banning ephedrine alkaloid are entitled to deference under the Administrative Procedure Act, and that judicial review is limited to the administrative record). The burden on the FDA to prove that a dietary supplement such as ephedra is adulterated before removing it from the market stands in marked contrast to the burden on applicants for approval of a new drug to demonstrate safety and efficacy in order to bring new pharmaceutical products to market in the first place.

98. *E.g.*, Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103-417, 108 Stat. 4325 (limiting the FDA's power to regulate dietary supplements as either food additives or new drugs).

99. *See* Request for Comments on FDA's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices, 59 Fed. Reg. 59,820, 59,821 (Nov. 18, 1994); Proposed New Drug, Antibiotic, and Biologic Drug Products Regulations, 48 Fed. Reg. 26,720, 26,733 (June

significant part of medical practice in some specialties, notably including oncology. Yet the FDA sharply curtails (insofar as the courts will permit)<sup>100</sup> manufacturers' efforts to disseminate information to physicians about off-label uses of drugs. If off-label uses of drugs threaten patient safety, then why permit them? On the other hand, if off-label uses do not threaten patient safety enough to prohibit them, then why not promote, rather than prohibit, the dissemination of any information about these uses that will help physicians make better choices for their patients?

These boundaries of FDA regulation, although puzzling from a consumer protection perspective, make considerably more sense from the perspective of promoting investment in drug trials. The FDA uses its powers as a market gatekeeper and as a censor of marketing claims not just to protect patients from untoward risks of harm, but also to motivate drug sponsors to generate valuable information about their drugs. The clinical trials that are necessary to generate this information are costly, time-consuming, and risky. The information that they provide is valuable, but trial sponsors are unable to capture much of that value. In fact, trial sponsors stand to lose revenue if trials indicate that their products are unsafe or ineffective for certain indications. Indeed, from the perspective of the manufacturer, rigorous clinical trials of off-label uses may be as likely to diminish the value of a particular product as to enhance it.<sup>101</sup> How to motivate firms to invest in generating this information in an honest, scientifically sound fashion is a major challenge for the law. By requiring that firms conduct rigorous clinical trials before bringing their products to market and before making promotional claims for their products, the FDA plays an important structural role in promoting a valuable form of biomedical R&D that private firms are undermotivated to perform on their own, while internalizing the costs of this R&D to the firms. By providing a system of independent expert scrutiny of the resulting data and certifying the safety and efficacy of tested products for particular indications, the FDA preserves public confidence in the integ-

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9, 1983); *Fed. Trade Comm'n v. Simeon Mgmt. Corp.*, 391 F. Supp. 697, 705–07 (N.D. Cal. 1975), *aff'd* 532 F.2d 708, 714–17 (9th Cir. 1976).

100. The courts in recent years have invalidated regulatory and statutory restrictions on the promotion of pharmaceutical products on First Amendment grounds. *See Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998); *Washington Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000); *Thompson v. Western States Med. Ctr.*, 535 U.S. 357 (2002).

101. A recent case in point is *Vioxx*, a product that had been approved by the FDA for treatment of pain and inflammation associated with osteoarthritis, menstruation, and rheumatoid arthritis and was generating sales in excess of \$2 billion per year before it was taken off the market by its sponsor, Merck. Merck undertook additional clinical trials in the hope of getting FDA approval to market *Vioxx* for prevention of recurrent colonic polyps. *See Rebecca S. Eisenberg, Learning the Value of Drugs—Is Rofecoxib a Regulatory Success Story?*, 352 *NEW ENG. J. MED.* 1285 (2005).

rity of the results while preserving them as proprietary information of the sponsor. Otherwise anomalous aspects of FDA regulation of new drug applications and promotional claims may be better understood as a response to this challenge than as a means of protecting consumers from purveyors of snake oil.

The control mechanisms that the FDA uses—setting barriers to bringing new products to market and limiting permissible promotional claims—make more sense as a way of motivating firms to conduct rigorous trials than as a way of protecting patients from risks of harm. After all, many patients already face substantial risks of harm from their diseases. By withholding new drugs from the market and blocking the dissemination to doctors of preliminary information about new uses for drugs that are already on the market, the FDA may well be increasing (or at least prolonging) these risks. Some commentators have sought to explain this paradoxical approach to health risks by noting that the FDA is more likely to be held accountable for harms that result from erroneous approval of a risky product than for harms that result from the operation of a disease that might have been treated effectively by a drug that was not yet approved.<sup>102</sup> Another explanation is that restricting the sale and marketing of drugs serves the distinct interest of getting firms to generate scientifically sound information about drug effects, which can only be generated through rigorous clinical trials. Because firms are eager to comply with whatever regulatory requirements stand in the way of bringing new products to market or making promotional claims for their products, deferring approval until the science is done may be the most effective way of promoting this interest.

In the case of *Washington Legal Foundation v. Friedman*,<sup>103</sup> the FDA advanced this argument explicitly in support of its restrictions on promotion of off-label use, in addition to the more conventional argument about protecting patients from health risks. That case involved a First Amendment challenge to FDA “Guidance Documents” from the early 1990s that restricted manufacturer promotion of off-label uses for approved drugs and devices through the distribution of reprints of publications and through manufacturer involvement in continuing medical education programs. The FDA claimed that distribution of these materials by product manufacturers amounted to unapproved labeling that rendered the products “misbranded” in violation of the Federal Food, Drug, and Cosmetic Act. The district court concluded that the regulated activities amounted to commercial speech and put the burden

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102. See, e.g., Mary K. Olson, *Pharmaceutical Policy Change and the Safety of Drugs*, 45 J.L. & ECON. 615, 618–20 (2002), and citations therein.

103. 13 F. Supp. 2d 51 (D.D.C. 1998).

on the FDA to show that the regulation was no more extensive than necessary to advance a substantial government interest.<sup>104</sup> The FDA advanced two interests in support of its regulation: (1) ensuring that physicians receive accurate and unbiased information so that they may make informed prescription choices; and (2) providing manufacturers with ample incentive to get previously unapproved uses “on label” by testing them and submitting them to the FDA for approval.<sup>105</sup> The court concluded that the first interest was inadequate to justify the intrusion on speech, but that the second interest—to provide an incentive for manufacturers to go through strict FDA trials to get off-label uses approved—was substantial.<sup>106</sup>

Two features of this litigation are particularly interesting. First, it is remarkable that the FDA explicitly advanced an argument for regulation as a means of promoting investment in clinical trials, even as a second line of defense, rather than sticking to traditional patient protection justifications. Second, it is remarkable that the court found the provision of incentives to conduct clinical trials a more persuasive justification for regulation than the conventional argument for protecting patients from risks. Plainly, the functions of FDA regulation have changed over time.

It remains to be seen whether the FDA will advance a similar argument in the *Abigail Alliance* case in support of its authority to keep drugs to treat terminally ill patients off the market pending completion of clinical trials. Given that the patient protection argument is particularly difficult to sustain when terminally ill patients seek access to unapproved products, the argument for R&D incentives may be more likely to succeed. It may also be a more candid account of the FDA’s regulatory goals.

## VI. WHY THE GOALS MATTER

Does it matter whether one views FDA regulation as a means of protecting patients from unsafe or ineffective products or as a means of promoting investment in clinical trials of drugs? Inasmuch as the information to be generated in clinical trials of drugs concerns safety and efficacy, the two goals may effectively converge for many purposes. Ultimately, the reason for promoting the particular types of R&D that FDA

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104. *Id.* at 71–72 (applying the test from *Central Hudson Gas & Electric v. Public Service Commission of N.Y.*, 447 U.S. 557 (1980)).

105. *Id.*

106. Although the regulations set forth in the FDA Guidance Documents directly advanced this interest, the court concluded that they were more extensive than necessary, because this interest could be addressed in a less burdensome manner by simply requiring full disclosure. *Id.* at 72–74.

regulation advances is not simply that we value research and innovation alone, but that we also value public health and safety and believe that sound clinical trials of new products will advance these goals. Of course, the same could be said of government involvement in biomedical research more generally. The reason that the budget of the National Institutes of Health (NIH) has grown, even as the budgets of other science agencies have languished, is that health-related innovation enjoys broader political appeal than other scientific pursuits. We value health, and we believe that high quality biomedical science will have public health payoffs. FDA regulation similarly promotes public health by promoting high quality scientific investigation of a particular sort—specifically, the conduct of scientifically rigorous clinical trials of drugs.

Understanding FDA regulation as a means of promoting innovation diminishes the force of the objection that it is paternalistic for the government to interfere in the drug choices of patients and physicians. Indeed, by inducing firms to provide better data about the effects of drugs in patients, FDA regulation permits patients and physicians to make better autonomous choices in the long run. In the short run, however, it limits the availability of drugs (and of information about drugs) pending the completion of clinical trials.

Regulation to motivate clinical trials thus presents a tradeoff between the interests of current patients and those of future patients. Such tradeoffs are familiar in the realm of innovation policy: for example, the patents that promote the development of new drugs tomorrow also permit firms to charge higher prices for currently available drugs today.<sup>107</sup>

An innovation-focused perspective on FDA regulation introduces a number of additional questions about how to best implement that mission. Although the goal of generating sound data about the effects of drugs in patients will often converge with the goal of protecting patients from unjustified risks of harm from unsafe or ineffective products, these goals might sometimes diverge. Some otherwise anomalous features of the current regulatory scheme make more sense from the revisionist perspective, while other features become harder to justify in this light.

1. *What Information?* Focusing on FDA regulation as a means of motivating the provision of information highlights the question of what information the system should aim to provide. This is an important question whether the function of regulation is understood from a patient-protection perspective or from an innovation-incentives perspective.

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107. Tradeoffs between the interests of current patients and future patients may be more troubling from the perspective of medical ethics. Indeed, clinical trials of drugs in patients often pose conflicts between the medical norm of providing the best possible care for any given patient and the goal of providing generalizable knowledge through the use of controlled trials.

Drugs are typically prescribed by doctors, paid for by health insurers, and consumed by patients. These parties vary greatly in their preferences for information about drugs, in their capacity to comprehend and use it, and in their ability to indicate demand for information in the market for drugs apart from regulation. Information dissemination by private firms is driven by profit considerations, which leads to gaps and distortions. The products that firms find worthwhile to advertise are typically relatively new drugs that are still under patent, available by prescription only, and covered by health insurance.

The doctors who prescribe drugs are the principal targets of information dissemination by pharmaceutical firms, although in recent years pharmaceutical firms have increasingly advertised their products directly to patients. Patients who follow the suggestions of advertisements will ask their doctors to prescribe particular products for them, perhaps assuming that their doctors are knowledgeable intermediaries who have studied available data about the products. Busy physicians, who are also the targets of aggressive marketing campaigns for these same products, may find it more expeditious to simply prescribe the products their patients seek rather than to investigate the data and exercise their own independent professional judgment about the value of these products.

The insurers that pick up the tab have an interest in controlling drug costs that might lead them to scrutinize the available data to determine whether drugs are worth prescribing. One might even imagine that insurers would be motivated to conduct clinical studies of drugs to determine their value and to decide whether to pay for them. Insurers presumably have access to patient populations and medical records, putting them in a good position to observe the relative benefits and harms of different treatments. They might also be in a good bargaining position to require proof of safety and efficacy from drug manufacturers as a precondition to covering their products. In practice, however, insurers do not currently play a significant role in either generating or demanding information about drug effects. Insurers rely heavily on physicians to make case by case prescription decisions, and strategies for getting physicians to control drug costs could backfire if they slow down the rate at which individual patients get in and out of the physician's office.

These complexities in the market for drugs suggest a number of reasons why market demand alone might fail to motivate the provision of reliable information about the effects of drugs in patients. But in the absence of such market demand, the question of what information is worth providing has no clear answer.

The Federal Food, Drug, and Cosmetic Act calls for the submission to the FDA of "full reports of investigations which have been made to

show whether or not such drug is safe for use and whether such drug is effective in use.”<sup>108</sup> Although this language leaves considerable room for agency discretion in fine-tuning the standards and determining whether they have been met, the statute unmistakably calls for decisions to be based on data from clinical trials that are subject to rigorous scrutiny rather than mere casual observation and individual clinical experience.<sup>109</sup>

The proper design of clinical trials depends on what questions one asks as well as on what sorts of data one counts as responsive to those questions. Deciding what questions to ask is not a purely scientific or technocratic judgment. It depends on what one wants to know, which is ultimately a matter of value-laden preferences. For example, in an earlier era the FDA generally preferred the submission of data from a homogeneous population of subjects that would permit isolation of drug effects from other variables, with the result that clinical trials were conducted primarily in white men. Today, the statute explicitly calls for regulators, in consultation with industry, to “develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials.”<sup>110</sup> Data gathered from a more diverse set of patients are noisier but may be more relevant to clinical practice, offering a better preview of how future patients will react to the drug.<sup>111</sup> Science alone cannot say which approach is better.

Another important judgment call concerns whether products should be tested against alternative treatments, placebos, or both. It is common in scientific experiments to use both positive and negative controls, yet clinical trials of drugs typically use only a negative control. The FDA has traditionally regarded placebo-controlled trials as a “gold standard” for establishing safety and efficacy. But placebo-controlled trials are considered unethical when patients face significant risks from a disease for which there is already an existing therapy, making it necessary to use the

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108. 21 U.S.C. § 355(b)(1)(A).

109. 21 U.S.C. § 355(d) calls for the submission of “adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use” and “substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof,” with “substantial evidence” defined as “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”

110. 21 U.S.C. § 355(b)(1)(G).

111. Data from trials in heterogeneous populations of research subjects may also suggest variations in drug response, leading to further trials in subgroups of responders of products that might otherwise have failed to win approval. A recent example is BiDil, a drug approved for the treatment of heart failure in self-identified black patients. See Jerry Avorn, *FDA Standards—Good Enough for Government Work?*, 353 NEW ENG. J. MED. 969 (2005).

existing therapy as a control in trials of new products for the same indication. From a scientific perspective, each approach has its advantages and its limitations.

Some observers have noted that the current system does a better job of testing short-term effects than long-term effects of drugs.<sup>112</sup> This is partly because of cost constraints involved in monitoring long-term effects, and partly because it is easier to motivate firms to comply with pre-market testing requirements that stand in the way of making sales than it is to get them to continue testing products after they are on the market. This focus on clinical trials in the pre-marketing stage limits the information that is generated. Such trials typically involve no more than a few thousand selected patients using a product over a period of months, and thus fail to reveal long-term effects of a drug when it is prescribed across a large population under real-life conditions. Post-marketing studies are more likely to reveal information about rare side effects, long-term effects, and drug interactions.

Viewing FDA regulation as a means of promoting the provision of information, it might make sense to shift the emphasis toward more post-marketing studies under regulatory supervision, instead of requiring definitive clinical test results before a product may be sold. In fact, in recent years the FDA has made increasing use of postmarketing requirements for continued testing of drugs.<sup>113</sup> One example has been the practice of approving the sale of new products under “fast-track” procedures while postmarketing studies continue, in the interest of getting products to market more quickly for treatment of life-threatening conditions such as cancer and AIDS. Congress endorsed this innovation in the Food and Drug Modernization Act of 1997.<sup>114</sup> The FDA also sometimes enters into agreements with sponsors to conduct post-marketing studies in the course of negotiations over the approval of a new product that is not on a fast-track. But sponsor compliance with post-marketing study requirements has been poor, revealing a serious pragmatic constraint on the FDA’s leverage over firms once their products are on the market.<sup>115</sup>

From the manufacturer’s perspective, once a product is on the market further testing in long-term trials is potentially very risky. Consider

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112. See, e.g., U.S. GOV’T ACCOUNTABILITY OFFICE, DRUG SAFETY: IMPROVEMENT NEEDED IN FDA’S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS, GAO-06-402 (2006); JAY S. COHEN, OVERDOSE: THE CASE AGAINST THE DRUG COMPANIES—PRESCRIPTION DRUGS, SIDE EFFECTS, AND YOUR HEALTH (2001).

113. For a critical review of this development, see 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 (2006).

114. Codified in pertinent part at 21 U.S.C. § 356.

115. DEP’T OF HEALTH & HUMAN SERVS. OFFICE OF INSPECTOR GEN., FDA’S MONITORING OF POSTMARKETING STUDY COMMITMENTS (2006).



the NIH Women's Health Initiative study on the effects of hormone replacement therapy (HRT) on the risk of heart disease in post-menopausal women.<sup>116</sup> Although the FDA had only approved the use of HRT for relief of menopause symptoms, prior observational studies had suggested that women who take HRT have a lower risk of heart disease. This evidence, although not definitive, was good enough to bring about widespread off-label prescription and use of HRT for the purpose of reducing the risk of heart disease. HRT manufacturers, although formally prohibited from actively promoting HRT for this untested purpose, nonetheless enjoyed significantly expanded sales from prescriptions in reliance on the results of the prior observational studies, and stood to gain little from subjecting doctors' beliefs in the benefits of its product to more rigorous tests. When the NIH, not the manufacturer, finally conducted a long-term, randomized, controlled study involving over 16,000 patients, early results indicated an *increased* risk of heart disease (as well as increased risks of other diseases) in women receiving HRT. While this information is undoubtedly valuable to patients, physicians, health insurers, and policy makers, it has sharply reduced sales of Prempro, a widely used HRT.<sup>117</sup> In this case, government funding provided valuable and credible information that the product's manufacturer had little incentive to uncover on its own.

Sometimes firms conduct post-marketing studies of approved drugs in the hope of getting supplemental NDAs for new indications, despite the costs and risks. A striking recent example of both the costs and risks is Merck's trial of Vioxx—a product previously approved by the FDA for treatment of specific types of pain and inflammation<sup>118</sup>—for the supplemental indication of preventing recurrence of colonic polyps. Vioxx sales were running at \$2.5 billion per year before Merck removed it from the market after observing cardiovascular side effects in the course of these post-marketing studies.<sup>119</sup>

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116. Writing Group for the Women's Health Initiative Investigators, *Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results From the Women's Health Initiative Randomized Controlled Trial*, 288 JAMA 321 (2002). More recent results are equivocal, suggesting that the risks and benefits of HRT may vary with age and years since menopause. J.E. Rossouw et al., *Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause*. JAMA 2007;297:1465–1477.

117. According to a front page story in the New York Times, the manufacturer of Prempro (Wyeth) estimates that the number of women taking Prempro fell from 2.7 million to 1.5 million following the announcement of the study results. Gina Kolata et al., *Menopause Without Pills: Rethinking Hot Flashes*, N.Y. TIMES, Nov. 10, 2002, at A1.

118. See FDA, COX-2 Selective (Includes Bextra, Celebrex, and Vioxx) and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), <http://www.fda.gov/cder/drug/infopage/COX2/default.htm> (last visited Feb. 22, 2007).

119. See Barbara Martinez et al., *Merck Pulls Vioxx From Market After Link to Heart Problems*, WALL ST. J., Oct. 1, 2004, at A1. The trial results are reported in Robert S. Bresalier et al.,

Why would Merck put the revenues from an already successful product at risk by conducting an additional clinical trial? The extensive media attention paid to Vioxx offers a rare glimpse behind the scenes of such decision-making,<sup>120</sup> revealing that marketing considerations and FDA oversight both played significant roles. The ostensible purpose of the study was to allow Merck to expand the market for Vioxx to include patients at risk of recurring colonic polyps. Although doctors were free to prescribe Vioxx off-label for this purpose, more aggressive marketing might have been necessary to get doctors to adopt an expensive drug, for a prophylactic indication, against a relatively minor condition. Merck needed FDA approval before it could actively promote Vioxx for this new indication. Moreover, a similar study was already underway for Pfizer's rival product, Celebrex,<sup>121</sup> threatening to put Merck at a marketing disadvantage if Celebrex were approved for an indication that remained off-label for Vioxx. Another purpose of the study, less touted but perhaps no less important, was to investigate (and hopefully put to rest) early concerns about the safety of Vioxx. Data from an early study comparing Vioxx to naproxen suggested an increased risk of cardiovascular events for patients receiving Vioxx.<sup>122</sup> Although Merck took the optimistic position at the time that this difference reflected a protective effect of naproxen rather than a toxic effect of Vioxx,<sup>123</sup> both Merck and the FDA thought the cardiovascular effects of Vioxx called for further study.<sup>124</sup> Merck's marketing executives were reluctant to conduct a trial focused on cardiovascular effects directly for fear of signaling concerns about the product, and preferred to observe cardiovascular side effects in a study designed to prove the value of the product for additional indications.<sup>125</sup>

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*Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial*, 352 NEW ENG. J. MED. 1092 (2005).

120. See, e.g., Alex Berenson et al., *Despite Warnings, Drug Giant Took Long Path to Vioxx Recall*, N.Y. TIMES, Nov. 14, 2004, at C1; Martinez, *supra* note 119.

121. Gideon Steinbach et al., *The Effect of Celecoxib, A Cyclooxygenase-2 Inhibitor, in Familial Adenomatous Polyposis*, 342 NEW ENG. J. MED. 1946 (2000); Scott D. Solomon et al., *Cardiovascular Risk Associated with Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention*, 352 NEW ENG. J. MED. 1071 (2005).

122. Claire Bombardier et al., *Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*, 343 N. ENG. J. MED. 1520 (2000). Naproxen is sold under the brand name "Aleve".

123. *Id.* at 1526; Peter S. Kim et al., *Rofecoxib, Merck & the FDA*, 351 NEW ENG. J. MED. 2875 (2004).

124. See Berenson et al., *supra* note 120.

125. *Id.* Some observers have criticized the FDA and Merck for failing to pursue a study focused directly on cardiovascular effects. Eric J. Topol, *Failing the Public Health: Rofecoxib, Merck & the FDA*, 351 N. ENGLAND J. MED. 1707 (2004). Such a study, however, would have been less informative than a study that tests efficacy as well as safety. In fact, the study revealed that Vioxx is effective in preventing recurrence of colonic polyps. Information about

The fact that Merck undertook such a long-term post-marketing study suggests that the system sometimes works to motivate the development of rigorous information, even at considerable risk of undermining the commercial interests of sponsors. On the other hand, the disastrous outcome for Merck might give other drug manufacturers pause about undertaking postmarketing trials of successful products in the future.

A significant limitation of the FDA regulatory system as a driver of information provision is that it only works when the manufacturer can recover the cost of obtaining the information, which usually means that sponsors conduct studies only on drugs with some remaining patent life. Otherwise, the market for information-laden drugs fails for the same reasons that markets for other information goods fail: competitors can share in the benefits of the information without sharing in the costs of producing it.<sup>126</sup> Suppose the manufacturer of an unpatented vitamin or dietary supplement believes that it could increase demand for its product by conducting clinical trials to convince skeptics that it is safe and effective. At best, the seller would have to share the expanded market with competitors who did not share in the cost of information provision. Worse, the trials might show that the product is unsafe or ineffective, causing loss of sales. The trials thus look like a poor investment, even though consumers of the product might value the information greatly. The provisions in the Hatch-Waxman Act conferring years of exclusivity before a generic competitor may enter the market through use of an ANDA (as opposed to the costlier NDA) are an effort to limit this sort of free-riding on expensive data for products that are no longer under patent. One could expand this approach to promote the testing of other unpatented products, such as vitamins, although consumers who are accustomed to buying such products at competitive prices might object to the higher prices for products available from a sole source. But while market exclusivity may help a firm to capture the benefits of favorable clinical trial results, it does nothing to help a firm recover from the revenue loss associated with unfavorable trial results.

Weaker regulation of vitamins and dietary supplements may make sense given the inability of manufacturers to capture the value of clinical trials. If dietary supplements were subjected to the same regulatory standards as patented drugs, the most likely result would not be improved

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the side effects of a drug is only meaningful in the context of information about its therapeutic benefits, permitting users to weigh risks against benefits.

126. Generic drugs also require FDA approval, but generic equivalents of previously approved products can win approval through a streamlined (and considerably cheaper) abbreviated new drug application (ANDA) without having to comply with the full regulatory requirements for a standard new drug application (NDA). 21 U.S.C. § 355(j).

information provision, but the disappearance of these products from the market. It may also be a sensible response to the information preferences of the consumers of these products: consumers who buy ginseng might care less about clinical trials conducted in accordance with modern science than they care about extensive prior use in China over a period of many centuries. A benefit of the current uneven regulatory regime is that consumers often have a choice between costly, information-rich pharmaceutical products and less expensive dietary supplements that may be sold without the burdens and benefits of costly clinical trials.

2. *Data Disclosure.* One aspect of the current regulatory regime that merits criticism when considered from the information provision perspective is the treatment of data submitted to the FDA as proprietary information of the sponsor not subject to public disclosure. The pharmaceutical industry has long taken the position that data from clinical trials of drugs are a trade secret belonging to the submitting firm, and the FDA has consistently supported this position<sup>127</sup> and withheld the data from public disclosure as a matter of administrative practice,<sup>128</sup> although the statutory language invoked in support of this position is ambiguous.<sup>129</sup>

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127. Although the FDA does not disclose the underlying data, it requires disclosure of certain information in the labeling of approved products. Moreover, in recent years the FDA has begun putting more information about approved products up on its website, including analyses of the data from clinical trials by FDA staff. *See, e.g.*, FDA, Label and Approval History, [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label\\_ApprovalHistory](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory) (last visited Feb. 22, 2007) (information about Vioxx).

128. *See, e.g.*, Public Information, 39 Fed. Reg. 44601, at 44611–12 (Dec. 24, 1974) (reviewing public comments on proposed regulations to implement the Freedom of Information Act) (“The Food and Drug Administration has on numerous occasions testified before Congress that current statutory prohibitions prevent disclosure of useful information contained in the agency’s files, and particularly, data relating to the safety and effectiveness of drugs. The Food and Drug Administration cannot change the law, and thus is bound by the present provisions until Congress acts.”); Public Information, 42 Fed. Reg. 3094, 3106 (Jan. 14, 1977) (noting that the FDA has treated data from clinical trials as a trade secret since 1938); *Anderson v. Dep’t of Health & Human Servs.*, 907 F.2d 936 (10th Cir. 1990); *Pub. Citizen Health Research Group v. FDA*, 997 F. Supp. 56 (D.D.C. 1998).

129. Proponents of trade secrecy have relied upon § 301(j) of the Federal Food, Drug, and Cosmetic Act, which prohibits:

The using by any person to his own advantage, or revealing, other than to the Secretary or officers or employees of the Department, or to the courts when relevant in any judicial proceeding under this Act, any information acquired under authority of section [505] . . . concerning any method or process which as a trade secret is entitled to protection.

21 U.S.C. § 331(j). It is by no means obvious from the statutory language that “any method or process which as a trade secret is entitled to protection” includes data from clinical trials, although the longstanding administrative practice would make it difficult to adopt a narrower reading of the provision at this point. *See* James T. O’Reilly, *Knowledge is Power: Legislative Control of Drug Industry Trade Secrets*, 54 U. CIN. L. REV. 1 (1985); Richard S. Fortunato, Note, *FDA Disclosure of Safety and Efficacy Data: The Scope of Section 301(j)*, 52 FORDHAM L. REV. 1280 (1983–84).

Amendments to the Federal Food, Drug, and Cosmetic Act as part of the Hatch-Waxman Act of 1984 appear to require that safety and efficacy data for a drug be made available to the public, “unless extraordinary circumstances are shown,” as soon as the Hatch-Waxman periods of data exclusivity have expired and an ANDA “could be made effective if such an application had been submitted.”<sup>130</sup> So far, however, the industry has successfully resisted a plain meaning interpretation of this provision.<sup>131</sup>

Trade secrecy and FDA regulation are intertwined at a number of levels. At least as a historical matter, pre-Hatch-Waxman, an important component of the value of safety and efficacy data from the perspective of drug manufacturers lay in the fact that it was required to overcome regulatory entry barriers.<sup>132</sup> The Federal Food, Drug, and Cosmetic Act requires the submission of “full reports”<sup>133</sup> of clinical trials to comply with the requirements for an NDA, which has long been understood to require submission of the underlying data rather than just published summaries. If competitors could gain access to the data, they could use it to submit their own NDAs to the FDA to bring generic versions of previously approved products to market without having to incur the cost and risk of doing their own trials.

This concern about free riders using publicly available data to get approval to sell a generic product in competition with a pioneer drug was arguably more substantial prior to the Hatch-Waxman Act than it is today. Under current law, generic competitors are effectively permitted to rely upon data previously submitted to the FDA for a bioequivalent product through the use of an ANDA once the statutory periods of data exclusivity have expired.<sup>134</sup> It is possible that a generic competitor might use publicly available data to submit its own full NDA (as distinguished from the streamlined ANDA) prior to the end of the data exclusivity period if all the listed patents have expired or are invalid, but the Hatch-Waxman Act does not require public disclosure until the time when an ANDA could become effective.<sup>135</sup> The FDA will not approve a generic product on the basis of an ANDA until applicable data exclusivity periods and patents have expired. At that point, with or without disclosure of the underlying data, current law permits free riding on prior studies through use of an ANDA. The generic firm need only

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130. Section 104 of the Hatch-Waxman Act, 98 Stat. 1597 (1984) (codified as amended at 21 U.S.C. § 355(l)).

131. See Jane A. Fisher, *Disclosure of Safety and Effectiveness Data under the Drug Price Competition and Patent Term Restoration Act*, 41 FOOD DRUG COSM. L. J. 268 (1986).

132. O'Reilly, *supra* note 129.

133. 21 U.S.C. § 355(b)(1)(A). See *supra* text accompanying note 108.

134. 21 U.S.C. § 355(j)(5)(F)(ii).

135. 21 U.S.C. § 355(l)(5).

show that its product is bioequivalent to a previously approved product and has no regulatory need to replicate the data through its own trials. By permitting substantial free-riding even without access to the underlying data, the Hatch-Waxman Act has thus taken the wind out of the sails of an argument against data disclosure that rests upon protection from free riders.<sup>136</sup>

The social benefits of disclosure of data from clinical trials are considerable. Publicly available data would permit patients, doctors, and insurers to make better choices of drugs. To the extent that data disclosure is valuable to these customers, one might expect them to exert market pressure on firms to provide it. Indeed, trade secrecy is a tricky strategy for information-dependent products like drugs, because firms need to make some disclosure of product information in order to capture its value. On the other hand, firms might be reluctant to disclose negative data that would diminish sales of their products. Trade secrecy allows firms to pursue a strategy of selective disclosure of favorable information from clinical trials, although perhaps with some loss of credibility for their claims.

FDA regulation may enable firms to sustain trade secrecy for competitively valuable information while still capturing some of its value to customers. FDA approval, in consultation with panels of independent experts, serves a certification function that enhances the credibility of informational claims about products while preserving substantial secrecy of the underlying data. FDA regulation combines bureaucratization of study design and data analysis with a system of scientific peer review and certification of undisclosed data. In the process, it standardizes the data that is collected and the format in which summary information is disclosed to the public, clarifying and simplifying the information given to a public that is unable to evaluate the data for itself. FDA personnel review the data, and some portions of the data may be disclosed to outside experts to assist the FDA in evaluating the safety and efficacy of the product. The FDA discloses considerable information to the public along with its conclusion that it finds the product safe and effective for a particular indication, including approval history, supporting analyses by FDA staff, and correspondence,<sup>137</sup> but the underlying data are not disclosed. Some disclosure of data occurs in summary form through the required labeling that must accompany the product in the market. The audience to whom these disclosures are directed is clinical decision-

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136. It is also possible that the data could be used to secure regulatory approval to sell generic products in foreign markets.

137. See Press Release, FDA, FDA Launches New Easy-to-Use Drug Information Web Site (Mar. 3, 2004), <http://www.fda.gov/bbs/topics/NEWS/2004/NEW01031.html>.

makers. In the case of a product that is available by prescription only, the disclosure in the labeling must be provided to prescribing physicians. In the case of an OTC product, it must be provided to patients and written in terms that are meaningful to them. The sponsors of a clinical trial, or the doctors and scientists carrying out the trial, might make further disclosures through publications or press releases, but they typically do not disclose the raw data.

From a patient protection perspective, this approach may be good enough, although it can be criticized as depriving patients and physicians of information that some of them might choose to scrutinize with greater care to make fully informed decisions. As a practical matter, the provision of summary information in the product label may well be all that most of these information users want.

But to the extent that FDA regulation is justified as a means of promoting the generation of socially valuable information, keeping the resulting information secret seems to restrict its social value. The data may, for example, alert other firms to hazards associated with a class of products, highlight the relative virtues of competing products, or point to potential new uses that merit further investigation. Secrecy permits firms to withhold this value from competitors, while exploiting it for themselves. But secrecy carries a considerable social cost. Public availability of data from clinical trials would allow firms to learn from each other's experience so that they could design better products and conduct better trials in the future. It would spare firms from having to continuously reinvent the wheel. It would steer them away from carrying out costly trials of products that are likely to fail, potentially bringing down the staggering average costs of new drug development.<sup>138</sup> It would permit reanalysis of data by skeptical competitors in ways that might challenge the spin selected by the product's sponsor, and facilitate meta-analysis of aggregated data from multiple studies of related products.

The loss from secrecy is likely to be compounded as progress in information technology opens up greater possibilities for data mining across numerous studies. Treating data as proprietary makes it difficult to analyze data from more than one product at a time. Combining data from multiple studies could provide powerful information about side effects and toxicities that are too rare to give rise to statistically significant observations in a single study limited to a few thousand patients. Although some toxicities are drug specific, and aggregation will thus not offer any advantage, other toxicities arise from variability across patients in drug metabolism enzymes and are likely to give some patients similar problems with multiple drugs. Such effects might be easier to observe by

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138. See *supra* note 15 and sources cited therein.

looking at results from multiple studies, particularly as the field of pharmacogenomics advances, as information technology improves, and as a growing understanding of the genetic basis of disease and drug response makes it possible to direct queries to data from multiple studies of different drugs in different patient populations.

Public disclosure would subject the basis for regulatory decisions to scrutiny, helping to ensure that decisions are well-grounded scientifically. It would permit independent analysis by scientists and institutions that do not share the agenda of the sponsor, providing a valuable check on distortions that arise from the wish to profit from hoped-for product sales. It might also provide answers to questions that neither the sponsor nor the FDA had thought to ask.

Although assurances of confidentiality for submitted data are not uncommon in the context of health and safety regulation,<sup>139</sup> government initiatives to promote innovation often call for eventual disclosure of new data. The patent system provides for full disclosure of patent specifications,<sup>140</sup> and judicial opinions celebrate this disclosure of information pertaining to patented technology as a means of promoting further innovation that provides a “quid pro quo” for the patent monopoly.<sup>141</sup> Sponsored research programs also sometimes call for public disclosure of data, although such requirements may face resistance from investigators with an interest in restricting access to data to their collaborators. The National Institutes of Health recently issued a statement on data sharing that requires all grant applicants seeking \$500,000 or more “to include a plan for data sharing or state why data sharing is not possible” as a part of their grant applications.<sup>142</sup> They cite a compelling list of arguments in support of data sharing, including reinforcing open scientific inquiry, facilitating new research, encouraging diversity of analysis and opinions, enabling the exploration of topics not envisioned by the original investigators, and permitting the creation of new data sets that combine data from different sources.

The FDA is sitting on a treasure trove of data that could accelerate the pace of pharmaceutical R&D, and is withholding it from public scrutiny under questionable statutory authority based on a longstanding administrative practice that has outlived its original justification.

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139. See *Ruckelshaus v. Monsanto Co.*, 467 U.S. 986 (1984); Thomas O. McGarity & Sidney A. Shapiro, *The Trade Secret Status of Health and Safety Testing Information: Reforming Agency Disclosure Policies*, 93 HARV. L. REV. 837 (1980).

140. 35 U.S.C. §§ 112, 122(b).

141. See, e.g., *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 484 (1974) (citing *Universal Oil Prods. Co. v. Globe Oil & Refining Co.*, 322 U.S. 471, 484 (1944) (Disclosure is “the *quid pro quo* of the right to exclude.”)).

142. NIH, Final NIH Statement on Data Sharing (Feb. 26, 2003), <http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html>.



3. *The Trigger for Approval.* Another question that emerges from re-considering FDA regulation as a means of promoting provision of information concerns appropriate requirements for new product approvals. The current requirement of demonstrating safety and efficacy prior to approval follows tautologically from the goal of protecting patients from unsafe or ineffective products, although not necessarily from a more broadly articulated goal of protecting the health of patients. But to the extent that regulation serves a distinct goal of promoting the provision of information, with the mechanism of premarket approval serving to exploit the greater leverage that the FDA holds over drug developers at this stage, it might be argued that the submission of sufficient data from rigorous testing should be the trigger for approval, even if the data tell an equivocal story about safety and efficacy.

This argument invites a number of objections that highlight the complex role played by the FDA in the current regulatory scheme. The current focus on safety and efficacy not only frames the inquiry but also guides determinations of how much evidence is necessary to meet the standard. Results from earlier studies may reveal limitations that prompt requirements for further studies. The endpoint of the inquiry is a moving target that cannot easily be specified in advance.

Moreover, FDA approval currently plays an important certification role that would be lost if approval were no longer contingent upon satisfaction of a standard for safety and efficacy but merely upon submission of data. In the current system, the data from clinical trials are proprietary, and FDA certification is therefore an important signal about what the data reveal. The fact that FDA scientists and their expert advisors have determined that a product is safe and effective for a particular indication is a valuable proxy for informed decision making by patients, doctors, payors, and policy makers. If product approval ceased to be a signal of safety and efficacy and meant nothing more than that the pertinent data were on file with the agency, the fact of FDA approval would lose this value, although other certification mechanisms could be substituted.

Some critics of the FDA have proposed that the function of certifying drugs as safe and effective could be performed by private firms rather than by a government agency, much as the American Automobile Association (AAA) certifies the cleanliness of roadside motels and Underwriters' Laboratories (UL) certifies the safety of electrical products.<sup>143</sup> But the recent history of scandals in the accounting industry highlights problems with relying on private experts to certify

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143. *E.g.*, HENRY I. MILLER, *TO AMERICA'S HEALTH: A PROPOSAL TO REFORM THE FOOD AND DRUG ADMINISTRATION* (2000).

the quality of information generated by their clients. The firms with the most pertinent expertise (e.g., contract research organizations that currently specialize in designing and conducting clinical trials of drugs on behalf of pharmaceutical firms) may have or seek other profitable dealings with the firms whose data they are certifying, calling into question the trustworthiness of the review. As drug development and the selection of drugs for particular patients becomes more specialized with advances in pharmacogenomics, the certification function is likely to become more important and complex. Scientific credibility is difficult to establish and fragile to maintain, cautioning against radical departure from a system that enjoys some current credibility.

4. *Alternative Mechanisms.* We currently look primarily to private firms to generate information about the effects of drugs in patients, relying on regulation to constrain their palpable incentives to cheat in developing and selectively disclosing information in order to sell more of their products. But this is not the only option.

Rather than compelling private sponsors to conduct their own clinical trials and allowing them to control access to the resulting data, one might use publicly-funded clinical trials (such as the HRT study funded by NIH) to generate information for the public about the effects of drugs. Currently the National Center for Comparative and Alternative Medicine (NCCAM) has conducted rigorous clinical trials on some popular herbal remedies and nutraceuticals, such as echinacea, glucosamine/chondroitin, and St. John's wort,<sup>144</sup> which were allowed to reach the market without testing for safety and efficacy. Since these products are typically unpatented, it is unlikely that private manufacturers would be willing to conduct costly clinical trials even if they were required as a condition for continuing to market the products. These NCCAM trials may indicate what we could expect from a system that leaves clinical trials of minimally regulated products to the government.

Ultimately, of course, there are limits to our political will to tax ourselves to pay for clinical trials. From a taxpayer perspective, a significant virtue of the current system is that it puts the costs of clinical trials on drug companies and the consumers who use the specific drug, and not on the public as a whole. Perhaps public resources should be deployed selectively to fortify the information base in areas where regulation is unlikely to induce private firms to conduct the necessary trials. This consideration might be one way of explaining the sometimes criticized distinction in current law between minimally regulated dietary supple-

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144. Research and clinical trial results may be accessed through the website of the National Center for Comparative and Alternative Medicine. NCCAM, Research Results, <http://nccam.nih.gov/research/results/> (last visited Feb. 22, 2007).

ments (such as vitamins and herbal remedies) and heavily regulated drugs. Although the distinction makes little sense from a consumer protection perspective, from the alternative perspective of promoting the development of information it makes sense to focus regulation on products that are potentially lucrative enough to allow sponsors to recover the costs of regulatory compliance. Imposing similar burdens on unpatented vitamins and herbal remedies that are sold in competitive markets would generate no further information, but would simply lead to the withdrawal of these products from the market. By placing the burden on the government to show that these products are unsafe and relying on the government to pay for the testing, we pay lip service to consumer protection while preserving markets for information-poor products that some consumers nonetheless want to buy.

Another obvious alternative is the tort system. Fear of tort liability for the sale of unsafe products should give firms some motivation to learn about the effects of drugs in patients and to withhold from the market products with risks that plainly outweigh their benefits. Moreover, at least in theory, the prospect of tort liability for failure to warn about product risks should give firms an incentive to disclose these risks to the public. On the other hand, given that tort law places the burden of proof upon plaintiffs, drug manufacturers might minimize their liability exposure by remaining ignorant and keeping consumers ignorant of the effects of their products. Concerns about tort liability would presumably aggravate the downside risk of conducting trials that could expose otherwise unsuspected toxicities, deterring firms from learning more about their products rather than motivating them to do further tests. Reliance on the determinations of inexpert juries adds more uncertainty to the system, making tort liability a clumsy vehicle at best for motivating the development of sound information about drug effects.

## CONCLUSION

As traditionally understood, the function of the FDA has been to protect consumers from dangerous or fraudulently marketed products. But as the practices and statutory authorities of the FDA have evolved, the agency has also come to play an important role in structuring incentives for biopharmaceutical innovation. These two functions are not entirely distinct from one another, and they have become closer over time. Sometimes the FDA uses its market gatekeeper role to perform a patent-like function of protecting innovators from competition from generic versions of new drugs. Regulatory sources of exclusivity have become more important as development times for new drugs have

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lengthened, cutting further into product patent terms, and as industry “evergreening” strategies to secure additional follow-on patents have encountered obstacles in the courts. Even the FDA’s core function of reviewing data from clinical trials to determine the safety and efficacy of drugs prior to market approval may be understood as a means of promoting costly investments in a particular form of R&D rather than simply as a means of protecting patients from untoward risks of harm. Indeed, some otherwise puzzling features of the FDA’s current regulatory authorities make more sense from the perspective of promoting provision of information than from the perspective of protecting patients. At the same time, examination of FDA regulations from the perspective of information provision raises new questions about the current system and may shed light on the strengths and weaknesses of particular mechanisms for regulating this important science-based industry.