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Rebecca S. Eisenberg

University of Michigan Law School, rse@umich.edu

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The Problem of New Uses

Rebecca S. Eisenberg, J.D.*

INTRODUCTION

Discovering new uses for drugs that are already on the market seems like it ought to be the low-lying fruit of biopharmaceutical research and development (R&D). Firms have already made significant investments in developing these drugs and bringing them to market, including testing them in clinical trials, shepherding them through the FDA regulatory approval process, building production facilities, and training sales staff to market them to physicians. By this point, the drugs have begun to enjoy goodwill among patients and physicians and casual observations in the course of clinical experience may point to potential new uses. One might expect that firms would be well-motivated to invest in the further clinical trials necessary to market their products for new uses. But in practice, the legal and economic environment for drug development complicates firms' incentives to pursue this research. Examining the problem of motivating firms to invest in rigorous testing of new uses for previously approved drugs provides an interesting window on this environment.

Drugs are information-rich chemicals that in many respects are more akin to other information products (such as databases) than they are to other chemicals (such as industrial solvents). Drugs are chemicals that have been tested extensively to determine their safety and efficacy in treating disease. It is the information derived from such testing that distinguishes the chemicals we call "drugs" from similar chemicals sold for other purposes, or even for the same purposes.¹ Creating new molecules has become relatively cheap, but determining which molecules are safe and effective for which therapeutic purposes has

* Robert & Barbara Luciano Professor of Law, University of Michigan Law School.

1. For example, dietary supplements sold in health food stores may be used for the same purposes as drugs, but with considerably less information to support their safety and efficacy. Current U.S. law nonetheless permits their sale, subject to very limited regulatory oversight. See 21 U.S.C.A. §§ 321, 331, 342, 343, 350 (West 1999 & Supp. 2004); 42 U.S.C. §§ 281, 287c-11 (2000). See generally Ctr. for Food Safety & Applied Nutrition, FDA, Regulatory Strategy for the Further Implementation and Enforcement of the Dietary Supplement Health and Education Act of 1994 (Nov. 2004), at <http://www.cfsan.fda.gov/~dms/ds3strat.html>.

remained stubbornly expensive, time-consuming, and risky.² Information about the effects of drugs has considerable social value as a resource for guiding doctors, patients, and insurers to make sound choices about which therapeutic products to use. But drug-developing firms capture only a fraction of this value. Drug companies make money by selling drugs, not by selling information about the effects of drugs. Information from clinical trials may enhance sales of drugs if it indicates that they are safe and effective, but it may also cause sales to plummet if it indicates that they are unsafe or ineffective. The social value of negative information about drugs is captured by consumers, payors, and sellers of substitute products rather than by the seller of the drug under study. From the perspective of a firm that has a lucrative pharmaceutical product on the market, rigorous clinical trials of new indications present a risk of generating results that could destroy the value of the product rather than enhance it.

A recent case in point is Vioxx, a product that was approved by the FDA for treatment of pain and inflammation associated with osteoarthritis, menstruation, and rheumatoid arthritis.³ Vioxx sales were generating \$2.5 billion per year when the drug was taken off the market by its sponsor, Merck, following the revelation of serious adverse cardiovascular effects in the course of a trial of Vioxx for the prevention of recurrent colon polyps.⁴ Early clinical trials had suggested adverse

2. A recent 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 eleven percent 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, 165, 166 (2003). Critics immediately challenged this estimate as inflating the true costs. See Ceci Connolly, *Price Tag for a New Drug: \$802 Million; Findings of Tufts University Study Are Disputed by Several Watchdog Groups*, WASH. POST, Dec. 1, 2001, at A10; Press Release, Pub. Citizen, Tufts Drug Study Sample Is Skewed; True Figure of R&D Costs Likely Is 75 Percent Lower (Dec. 4, 2001), <http://www.publiccitizen.org/pressroom/release.cfm?ID=954>; see also MERRILL GOOZNER, *THE \$800 MILLION PILL: THE TRUTH BEHIND THE COST OF NEW DRUGS* (2004).

More recently, a 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*, IN VIVO: BUS. & MED. REP., Nov. 2003, at 1, http://www.bain.com/bainweb/PDFs/cms/Marketing/rebuilding_big_pharma.pdf. These cost estimates, which include research and development (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.

3. See Ctr. for Drug Evaluation & Research, FDA Public Health Advisory: Safety of Vioxx (Sept. 30, 2004), http://www.fda.gov/cder/drug/infopage/vioxx/PHA_vioxx.htm.

4. See Barbara Martinez et al., *Merck Pulls Vioxx From Market After Link to Heart Problems*,

cardiovascular effects for Vioxx, but Merck took the position that the results were inconclusive and hoped that ongoing trials of the product for additional indications, culminating in supplemental FDA approval, would set these concerns to rest.⁵ Instead, further trials indicated that Vioxx did indeed significantly increase the risk of serious cardiovascular events.⁶ This is life-saving information that has considerable value from a public health perspective. Indeed, in a much-publicized study, one FDA scientist has estimated that from 1999 through 2003, approximately 27,000 heart attacks and sudden cardiac deaths could have been avoided if physicians had prescribed alternative medications instead of Vioxx.⁷ But from the perspective of Merck and its shareholders, this information has triggered a catastrophic loss of value.⁸ The social value of better information about the effects of drugs in patients can thus depart dramatically from its private value to firms that invest in clinical trials, making it difficult to rely on private markets to generate credible information. Profit-seeking firms face powerful incentives to develop and disclose information selectively, and perhaps even to delude themselves, in order to maximize product sales.⁹ Motivating firms to provide high quality information about the effects of

WALL ST. J., Oct. 1, 2004, at A1.

5. See Anna Wilde Mathews & Barbara Martinez, *E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage*, WALL ST. J., Nov. 1, 2004, at A1. The earlier results are reported in 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).

6. The study results are reported in Robert S. Bresalier et al., *Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial*, 352 N. ENG. J. MED. 1092, 1098 (2005). Although publicity has focused on the demonstration of cardiovascular risks, the study also found a reduction in the recurrence of colon polyps. See Gina Kolata, *Good Pill, Bad Pill: Science Makes It Hard To Decipher*, N.Y. TIMES, Dec. 22, 2004, at A1.

7. Memorandum from David G. Graham, Associate Director for Science, Office of Drug Safety, to Paul Seligman, Acting Director, Office of Drug Safety, Risk of Acute Myocardial Infarction and Sudden Cardiac Death in Patients Treated with Cox-2 Selective and Non-Selective NSAIDs (Sept. 30, 2004), <http://www.fda.gov/cder/drug/infopage/vioxx/vioxxgraham.pdf>; see Anna Wilde Mathews, *New Vioxx Study Projects Cases of Heart Attacks*, WALL ST. J., Oct. 6, 2004, at A2.

8. The results caused Merck to pull Vioxx off the market, forgoing \$2.5 billion a year in sales and causing its market capitalization to drop by \$26.8 billion. See Martinez, *supra* note 4.

9. Indeed, Merck faces allegations that it suppressed early warnings about the hazards of Vioxx. See Mathews & Martinez, *supra* note 5. Mathews and Martinez cite an internal email message from a Merck scientist that notes that “the possibility of increased CV [cardiovascular] events is of great concern”; adds parenthetically, “I just can’t wait to be the one to present those results to senior management!”; and suggests that patients with high risk of cardiovascular problems be kept out of the study so that the difference between patients receiving Vioxx and the others “would not be evident.” *Id.*

drugs in patients is thus a major challenge for the legal system.

In this Article, I examine three forms of legal regulation that affect the incentives of firms to invest in clinical trials: patents, FDA regulation, and trade secrecy. Although each of these legal regimes offers firms some protection from free riders who might otherwise use the information from clinical trials in competition with them, each has significant shortcomings as a regulatory mechanism for promoting the development of information about the effects of drugs through rigorous clinical trials.

Patent protection on drugs typically begins and ends too early to permit firms to capture the full value of subsequently developed information about drug effects. It therefore does a better job of motivating the initial R&D that is necessary to bring new products to market than it does of motivating the development of new information about old drugs. The discovery of a new use for an old drug might support a patent on a method of treatment, but such a patent offers little effective protection against generic competition once the drug itself is off-patent and may lawfully be sold for an older, unpatented use.

FDA-administered exclusivities do not begin to run until a drug is on the market, but they typically end before the expiration of patent protection. Additional exclusivity may later be obtained for conducting clinical trials of new uses of previously approved products, but like patents on new uses, these FDA-administered exclusive rights are limited to the new use and thus provide little protection from generic competition once the term of protection has expired for an older use of the same product. The most effective way that the FDA motivates investment in clinical trials is simply by demanding it as a precondition for approval of a New Drug Application (NDA). But once a drug is approved for a first indication, the permissibility of off-label sales dampens the incentives of firms to conduct further trials of additional indications. Such trials are not only costly, but also pose a risk of exposing previously unrecognized toxicities, thereby reducing rather than expanding product demand.

Trade secrecy mitigates this risk by allowing firms to suppress data from clinical trials, withholding its value not only from competitors but also from consumers who might otherwise demand less of the product. But trade secrecy greatly compromises the social value of the information as a resource for improving public health and for promoting further R&D. It also exposes drug companies and regulators to charges of bad faith and incompetence, compromising the signaling function of regulatory approval as a marker of safety and efficacy.

I. PATENTS

Patent law traditionally takes the lion's share of credit for motivating

investments in drug development. The pharmaceutical industry is famously dependent upon patent protection to support its R&D costs and has consistently advocated for stronger patent protection throughout the world.¹⁰ But patent law is better suited to protecting tangible products and processes than it is to protecting information. Although patent applicants are required to make enabling disclosures of how to make and use their inventions,¹¹ and judicial decisions celebrate the value of these disclosures as the *quid pro quo* for the patent right, the informational content of patent applications is generally treated as a spillover for the benefit of the public rather than as an object of protection in its own right.¹² Even as recent judicial decisions have opened up the patent system to protecting information technology,¹³ patents have remained unavailable for data.¹⁴

Nonetheless, patents on tangible products (such as drugs) and processes (such as methods of treatment) might motivate firms to invest in data production in order to develop markets for their inventions. Data from clinical trials of new uses might expand the market for drugs, and patents on drugs and methods of use might be used to exclude free riders from competing for these sales during the patent term. This allows firms to capture much of the value of successful trials that show their products to be safe and effective for particular purposes, although it does not allow them to capture the value of trials that show their products to be unsafe or ineffective. The value of data from unsuccessful trials accrues to consumers and insurance payors who forego purchasing the drug and perhaps also to competitors who develop and manufacture substitute products,¹⁵ all

10. 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, 1075-85 (1996).

11. 35 U.S.C. § 112 (2000).

12. See generally John N. Adams & Gwen Averly, *The Patent Specification: The Role of Liardet v. Johnson*, 7 J. LEG. HIST. 156 (1986) (reviewing eighteenth century decisions that emphasized the role of a robust patent disclosure standard in promoting the introduction of technical knowledge rather than merely the introduction of finished products).

13. *AT&T Corp. v. Excel Communications, Inc.*, 172 F.3d 1352 (Fed. Cir. 1999); *State St. Bank & Trust v. Signature Fin. Group*, 149 F.3d 1368 (Fed. Cir. 1998).

14. See Examination Guidelines for Computer-Related Inventions, 61 Fed. Reg. 7478 (Feb. 28, 1996). Copyright also provides no protection for data. See *Feist Publ'g Inc. v. Rural Tel. Serv. Co.*, 499 U.S. 340 (1991).

15. For example, the withdrawal of Vioxx from the market initially increased sales of Celebrex. See Scott Hensley, *Pfizer Is Early Winner as Vioxx Users Switch Drugs*, WALL ST. J., Oct. 6, 2004, at D13. Soon thereafter, however, the National Institutes of Health (NIH) suspended the use of Celebrex in clinical trials on the basis of data suggesting that it presents similar cardiovascular risks. See Press Release, NIH, NIH Halts Use of COX-2 Inhibitor in Large Cancer

without infringing the patent rights of the firm that paid for the trial.

Even for successful clinical trials, the term of the patent may be poorly timed to permit holders of patents on drugs to capture the value of the data, particularly for trials of new uses. Drug development necessarily involves the discovery of new compositions of matter before their therapeutic value can be definitively established through clinical trials.¹⁶ 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.¹⁷ This leads inventors to file patent applications on new molecules as soon as they can establish patentable utility for them, typically years before first commercial marketing of a drug.¹⁸ Under current law,¹⁹ patents expire twenty years after their filing dates,

Prevention Trial (Dec. 17, 2004), <http://www.nih.gov/news/pr/dec2004/od-17.htm>; Press Release, NIH, Use of Non-Steroidal Anti-Inflammatory Drugs Suspended in Large Alzheimer's Disease Prevention Trial (Dec. 20, 2004), <http://www.nih.gov/news/pr/dec2004/od-20.htm>. Prescriptions for Celebrex promptly plummeted. See Christopher Windham & Ron Winslow, *Prescriptions for Celebrex, Naproxen Drop Sharply*, WALL ST. J., Dec. 30, 2004, at A3.

16. For a description of the drug development process, see CTR. FOR DRUG EVALUATION & RESEARCH, FDA, FROM TEST TUBE TO PATIENTS: IMPROVING HEALTH THROUGH HUMAN DRUGS (1999), <http://www.fda.gov/cder/about/whatwedo/testtube-full.pdf>. See also *In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995) (noting that drugs are eligible for patent protection before they have met the standards for FDA approval).

17. A patent application is barred under § 102(b) of the Patent Act if the inventor fails to file within one year of first publication or other public use of the invention. 35 U.S.C. § 102(b) (2000). Moreover, the dilatory applicant who keeps the invention secret risks losing priority to another applicant who subsequently claims the same molecule if he is deemed to have "abandoned, suppressed, or concealed" the invention. *Id.* § 102(g)(1).

18. An invention must be useful in order to be patented. *Id.* § 101; see also *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 FDA to bring a new drug to market. *E.g.*, *In re Brana*, 51 F.3d at 1567-68 ("The Commissioner . . . confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. . . . FDA approval, however 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.") (citations omitted).

19. 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). See Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, LEGAL INSTRUMENTS—RESULTS OF THE

regardless of when they issue.²⁰ The Hatch-Waxman Act of 1984 provides for patent term extensions of up to five years to compensate for some of the time that the patent meter is ticking pending regulatory approval of a new drug, so long as the total remaining patent life after extensions does not exceed fourteen years from the date of approval.²¹ 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 lives appearing toward the end of the period under study.²² But sometimes the effective patent life for new drugs is far shorter, diminishing the time in which the basic drug patent permits a firm to capture the value of information it has generated about the drug.²³

URUGUAY ROUND vol. 31, 33 I.L.M. 1197 (1994); Uruguay Round Agreements Act, Pub. L. No. 103-465, 108 Stat. 4809 (1994) (codified as amended in pertinent part at 35 U.S.C.A. § 154 (West 2001 & Supp. 2004)).

20. 35 U.S.C. § 154(a)(2) (2000). For U.S. patent applications filed prior to 1995, the applicant may elect instead a term that begins with issuance of the patent and ends seventeen years later. *Id.* § 154(c)(1). The seventeen-year term sometimes permitted 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 prosecuted in series to obtain staggered patent terms. Recently, the Federal Circuit has become skeptical of this and other “evergreening” strategies for prolonging patent protection for drugs and has found ways to hold the later-issued patents invalid. *See, e.g., Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373 (Fed. Cir. 2003) (holding invalid later-issued patents deriving from the same parent application as expired patents on the antibiotic Augmentin on grounds of “double patenting”).

21. 35 U.S.C.A. § 156 (West 2001 & Supp. 2004). The period of extension may include half of the time spent in clinical trials before the firm submits 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. *Id.* § 156(c), (g)(1)(B), (g)(6).

22. Henry G. Grabowski & John Vernon, *Effective Patent Life in Pharmaceuticals*, 19 INT’L J. TECH. MGMT. 98 (2000).

23. For example, the antidepressant drug Paxil did not get to market until after its basic patent had expired. *See SmithKline Beecham Corp. v. Apotex Corp.*, 365 F.3d 1306, 1309 (Fed. Cir. 2004). Term extensions are unavailable after patents expire, 35 U.S.C. § 156(a)(1) (2000), although interim extensions may be obtained if it appears that the regulatory review period will extend beyond the term of the patent. *Id.* § 156(d)(5). The basic patent on a class of compounds including the molecule that was ultimately brought to market under the brand name Paxil, U.S. Patent No. 4,007,196 (issued Feb. 8, 1977), had a terminal disclaimer causing it to expire on October 14, 1992. (A terminal disclaimer is a surrender by the patent applicant of a portion of the patent term, usually entered to avoid a “double patenting” rejection of a patent that claims an obvious variation on a previously patented invention. *See Geneva Pharm.*, 349 F.3d at 1377-78. 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, 894 (Fed. Cir. 1985).) SmithKline Beecham brought a hemihydrate form of Paxil to market in

New information about the uses of a product will sometimes allow the developer to get a process patent. For example, clinical trials showing that a drug works for a new indication may support a process patent on a new method of treatment, even though the same drug has previously been used for another purpose.²⁴ But process patent claims that are limited to particular therapeutic uses are generally considered less valuable than product patent claims covering the drug itself because the process claims cannot be used to stop competitors from selling the same product for other uses.²⁵ In theory, the patent-holder could still enforce the process patent against patients who take the drug for the patented use, doctors who prescribe it for such use, pharmacists who fill the prescriptions, or competing manufacturers who urge any of these actors to substitute their bioequivalent generic versions of the product for the patent-holder's product in such prescriptions.²⁶ But these remedies are generally less satisfactory than an injunction that would stop a competitor from making the product entirely. It is more difficult to detect and prove infringing uses than it is to detect and prove infringing products, and it is less efficient to sue numerous patients and physicians than it is to sue a single manufacturer. Moreover, few industries prosper by suing customers,²⁷ and the marketing interests of the pharmaceutical

1993, following FDA approval of its NDA on December 29, 1992. Meanwhile, the firm had obtained a separate patent on the hemihydrate form of the molecule, U.S. Patent No. 4,721,723 (issued Jan. 26, 1988). This subsequent patent was still in effect on the FDA approval date and the firm selected this later patent for term extension. See 35 U.S.C. § 156(c)(4) (“[I]n 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 clinical trials more than a year prior to the filing date of the patent application had placed the invention in public use, giving rise to a statutory bar under 35 U.S.C. § 102(b). *SmithKline Beecham*, 365 F.3d at 1321. Historical information on the approval history of Paxil (and other drugs) is provided at Ctr. for Drug Evaluation & Research, FDA, *Drugs @ FDA*, at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/> (last visited Mar. 28, 2005) [hereinafter *Drugs @ FDA*].

24. See, e.g., *In re Marshall*, 578 F.2d 301, 304 (C.C.P.A. 1978) (reversing rejection of claim to method of using old compound to control weight, where prior art had disclosed method of using same compound to treat esophagitis, gastritis, peptic ulcer, and irritable colon syndrome, noting that “[i]f anyone ever lost weight by following the [prior art] teachings it was an unrecognized accident”).

25. See, e.g., *Allergan Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322 (Fed. Cir. 2003) (holding patent on new use of drug does not provide infringement remedy under Hatch-Waxman Act against generic competitor who seeks FDA approval to market same drug for a different use not covered by the patent); *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348 (Fed. Cir. 2003) (same).

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

27. A rare example of an intellectual property owner seeking to enforce its rights by suing customers is the Recording Industry of America, which has brought infringement actions against

industry are probably better served by soliciting physicians to write prescriptions than by suing them for contributory infringement of their patents.²⁸ Although patent-holders would rather sue generic competitors, sale of an unpatented product that is suitable for substantial non-infringing use is not patent infringement²⁹ unless the seller actively promotes an infringing use.³⁰ If the competitor merely brings the generic product to market for the old use, the fact that the product may be prescribed and used off-label for a patented new use is not enough to make the seller liable as an indirect infringer.³¹

II. FDA REGULATION

Although FDA regulation is typically understood to be a burdensome cost of drug development and rarely gets any credit for promoting biopharmaceutical R&D, FDA regulation in fact has come to play an important role in motivating firms to study the effects of drugs. FDA regulation fortifies the incentives of firms to invest in generating this socially valuable information in two ways: first, by requiring the submission of information as a precondition to bringing new products to market and to making marketing claims about products; and second, by conferring exclusive rights in the use of data submitted to the FDA for regulatory purposes. Because of their resemblance to the rights conferred by patents, I begin by considering the effects of FDA-administered exclusive rights.

A. FDA-Administered Exclusivities

FDA regulation sometimes provides patent-like rights in data from clinical trials by deferring approval of the products of generic competitors for the periods of time specified by statute. Some of these statutory provisions essentially provide for data exclusivity, deferring the time when other firms may rely on the pioneer's data in seeking regulatory approval for their own generic versions of the same drug,³² while others provide product market exclusivity in a new

individuals who download and share copyright-protected music. See Press Release, Recording Indus. Ass'n of Am., Music Industry Commences New Wave of Legal Action Against Illegal File Sharers (Dec. 3, 2003), <http://www.riaa.com/news/newsletter/120303.asp>.

28. For an unsettling account of the relationship between the pharmaceutical industry and the medical profession, see JEROME P. KASSIRER, *ON THE TAKE: HOW MEDICINE'S COMPLICITY WITH BIG BUSINESS CAN ENDANGER YOUR HEALTH* (2005).

29. 35 U.S.C. § 271(c).

30. *Id.* § 271(b).

31. See *C.R. Bard v. Advanced Cardiovascular Sys. Inc.*, 911 F.2d 670 (Fed. Cir. 1990).

32. See, e.g., 21 U.S.C.A. § 355(j)(5)(F)(ii), (iii) (West Supp. 2004).

product.³³ Data exclusivity can be the functional equivalent of product market exclusivity if the submission of data to the FDA is a condition for market entry and if the cost of regulatory compliance is prohibitive for a generic competitor.³⁴

The first statutory provision for FDA-administered exclusive rights in approved drugs was enacted as part of the Orphan Drug Act of 1983,³⁵ a legislative package designed to fortify incentives to develop treatments for rare diseases. The exclusivity provision of the Orphan Drug Act directs the FDA to grant seven years of market exclusivity for products to treat rare diseases and conditions affecting small populations,³⁶ later defined as fewer than 200,000 patients in the United States.³⁷ This is not merely a data exclusivity provision, but a statutory prohibition against approving another application for the same drug for the same disease for a period of seven years.³⁸ Although one might expect that products qualifying for this protection would have markets that are too small to be lucrative, in fact many products that enjoy exclusivity under the Orphan Drug Act have had large and profitable markets for off-label use.³⁹ The effect of market exclusivity under the Orphan Drug Act is similar to seven years of patent protection, although it does not preclude approval of either (1) another drug for the same disease or condition,⁴⁰ or (2) the same drug for another disease or

33. See, e.g., *id.* § 360cc(a) (West 1999 & Supp. 2004).

34. Indeed, even before Congress enacted the statutory exclusivity periods discussed in this section, FDA regulation provided significant protection from generic competition even after drugs went off-patent just by treating data from clinical trials as proprietary information belonging to the sponsor. 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 & COSMETIC L.J. 269, 273-76 (1985).

35. Pub. Law No. 97-414, 96 Stat. 2049 (1983) (codified as amended in various sections of 21, 26, 35, & 42 U.S.C).

36. 21 U.S.C.A. § 360ee(b)(2).

37. *Id.* § 360cc(a).

38. Specifically, the statute prohibits approval of “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 . . .” *Id.*

39. Examples of blockbuster products that have received orphan drug status include Taxol and AZT. The FDA provides cumulative lists of orphan drug designations and approvals. FDA, List of Orphan Designations and Approvals, at <http://www.fda.gov/orphan/designat/list.htm> (last visited Feb. 20, 2005).

40. FDA regulations define the statutory term “such drug” to mean a drug with the same “active moiety” and not “clinically superior.” 21 C.F.R. § 316.3(b)(13) (2004). This potentially provides a narrower range of exclusivity than a patent, which can sometimes define the invention quite broadly with claim language extending to cover a genus of structurally similar molecules. *Cf.* Berlex Labs. v. FDA, 942 F. Supp. 19 (D.D.C. 1996) (rejecting a challenge under Orphan Drug Act to the FDA’s approval of a competitor’s slightly different version of a biological product).

condition.⁴¹

In 1984, Congress added two more provisions for FDA-administered market exclusivity in the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the “Hatch-Waxman Act.”⁴² As part of a complex legislative compromise between the interests of research pharmaceutical firms and generic competitors, the Hatch-Waxman Act provided five years of exclusivity for new chemical entities not previously approved by the FDA⁴³ and three years of exclusivity for supplemental NDAs on previously approved products, such as new indications or other changes in a previously approved product that require conducting new clinical trials to win FDA approval.⁴⁴ In contrast to the exclusive rights to sell “such product for such use” conferred by the Orphan Drug Act, these Hatch-Waxman Act provisions merely confer data exclusivity, preventing the FDA from allowing generic competitors to obtain streamlined review of their applications through use of an abbreviated new drug application (ANDA) without having to submit a full new drug application.⁴⁵ Prior to passage of the Hatch-Waxman Act, generic competitors had faced prohibitive regulatory entry barriers when they were required to either conduct their own clinical trials of generic versions of their products or obtain permission to rely on data previously submitted by the brand name product manufacturer in order to get their products approved by the FDA. Because generic firms could not hope to recover this cost through sales at competitive prices, brand name drugs often continued to dominate the market even after their patents expired. In order to promote generic entry, the Hatch-Waxman Act provided that for off-patent drugs, generic versions could be approved upon a showing of bioequivalence to the previously approved product through use of an ANDA.

The five-year period of exclusivity for new chemical entities defers FDA approval of generic entry through the less costly ANDA route even if the product

41. This can be a significant limitation. *E.g.*, *Sigma-Tau Pharm. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002) (holding that orphan drug exclusivity for new indication for levocarnitine did not preclude FDA approval of generic versions of same product for older indications for which exclusivity had expired, notwithstanding that generic versions might be prescribed by physicians off-label for new indication that was still covered by exclusivity). The FDA’s lack of authority over off-label use of drugs is discussed further *infra* notes 59–60.

42. Pub. Law No. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of 21, 35 & 42 U.S.C.).

43. 21 U.S.C.A. § 355(j)(5)(F)(ii) (West Supp. 2004).

44. *Id.* § 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 seeks approval of a drug for new indications, or conducts clinical trials to determine whether a drug may safely be switched from prescription to over-the-counter (OTC) status.

45. The more extensive requirements for a full NDA are set forth in § 355(b)(1).

is not protected by patent, but it does not prevent a competitor from obtaining approval of an unpatented product 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.⁴⁶ In effect, this amounts to FDA-administered proprietary rights in data from clinical trials. Because the five-year period of data exclusivity for a new chemical entity begins with first market approval, it typically runs concurrently with patent protection. However, in some cases it may last longer,⁴⁷ providing a minimum five-year period of exclusivity even for unpatented products or for products that are covered by invalid patents.

The three-year period of data exclusivity for supplemental NDAs that require clinical trials to gain approval begins with the approval date of the supplemental NDA,⁴⁸ making it potentially advantageous to defer the filing of a supplemental NDA until a product approaches the end of its patent life in the hope of prolonging exclusivity. At that point, the firm might, for example, seek

46. The statute sets up a complex system for tracking patents covering approved drugs and for staying regulatory proceedings pending litigation of patent infringement claims. *See id.* § 355(b), (c), (j) (West 1999 & Supp. 2004). Holders of approved 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*. CTR. FOR DRUG EVALUATION & RESEARCH, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS [THE ORANGE BOOK] (24th ed. 2004), <http://www.fda.gov/cder/ob/docs/preface/ectablec.htm>. A competitor wishing to file an ANDA for a drug that is bioequivalent to the approved drug must make a declaration with respect to each of the patents listed in the *Orange Book* stating either (1) that the drug is not patented; (2) that the patent has expired; (3) that the patent will expire on a specified date; or (4) that the patent is either invalid or will not be infringed by the ANDA product (known as a "Paragraph IV certification"). If an ANDA filer makes a Paragraph IV certification, it must provide notice to the patent-holder and NDA filer (typically the same firm), along with a detailed statement of the factual and legal basis for the assertion that the patent is invalid or not infringed. § 355(j)(2)(B) (West Supp. 2004). The patent-holder then has forty-five days within which to bring an infringement action against the ANDA filer in order to prevent the FDA from approving the ANDA effective immediately under § 355(j)(5)(B)(iii). The Hatch-Waxman Act added to the Patent Act a new section, 35 U.S.C. § 271(c)(2) (2000), which makes it a technical act of patent infringement to file an ANDA for a drug claimed in a patent or the use of which is claimed in a patent. This was necessary in order to permit litigation of the issue of patent infringement before the generic product got to market, because Congress declared in § 271(e)(1) that use in clinical trials was not an act of patent infringement. If the patent-holder brings an infringement action within forty-five days, that triggers a thirty-month stay of FDA approval for the ANDA under 21 U.S.C.A. § 355(j)(5)(B)(iii) (West Supp. 2004) while the parties litigate the infringement issue.

47. *See supra* note 23 and accompanying text (discussing Paxil).

48. § 355(j)(5)(F)(iii).

approval to switch a product from prescription to over-the-counter (OTC) sales,⁴⁹ after first testing the product in patients to determine if they may safely self-administer the drug without the supervision of a physician in order to qualify for the additional period of exclusivity. A supplemental NDA may also be used to get approval to market a previously approved drug for a new use. Either way, 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 gain approval to sell the product as previously approved, or for previously approved indications.

This has proven to be a very significant limitation on the benefit of using a supplemental NDA to gain approval to market a drug for a new indication.⁵⁰ The three-year exclusivity does not preclude a generic competitor from using an ANDA to get approval to sell its version of the product for the original indication; further, once the generic version is available on the market, the FDA can do nothing to stop physicians from prescribing the generic product off-label for the new indication. Indeed, unless the new indication involves a different formulation of the product, state generic substitution laws may force the original innovator to lower its prices to meet the generic price to avoid substitution at the point of filling the prescription.⁵¹

The exclusivity that comes with a supplemental NDA is more effective in thwarting generic competition for a prescription to OTC switch. Gaining FDA approval to sell a drug in the OTC market will not preclude a generic competitor from filing an ANDA to sell the same product by prescription, but it may be difficult for the prescription generic to compete with the OTC branded product. Moreover, consumers may be more likely to select brand name products in the OTC market, while doctors and pharmacists, facing pressure from insurers to keep costs down, may be more likely to substitute cheaper generics in the prescription drug market.⁵²

The Food and Drug Administration Modernization Act of 1997⁵³ added a

49. 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), at http://www.klinegroup.com/6_2002815.htm.

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

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

52. Indeed, some insurers do not provide coverage of brand name products if generic equivalents are available. See, e.g., Univ. of Mo., *University of Missouri Faculty & Staff Benefits: Mandatory Generic Drug Substitution*, at <http://www.umssystem.edu/hrs/benefits/prescription/generic.htm> (last updated Oct. 15, 2004).

53. Pub. Law No. 105-115, 111 Stat. 2296 (codified as amended in scattered sections of 21, 26 & 42 U.S.C.). Although this provision was originally set to expire after five years, it has been

provision for six months of exclusivity as a reward for conducting pediatric trials of drugs.⁵⁴ 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, further deferring the time when the FDA might approve a competing generic product.

Each of these provisions confers exclusionary rights under the auspices of the FDA rather than the U.S. Patent and Trade Office. The FDA-administered rights are linked to submission and consideration of data from clinical trials of drugs for safety and efficacy and have the effect of rewarding firms that invest in rigorous clinical trials by protecting them from competition. But there are gaps in the scope of exclusion, particularly in the context of clinical trials of new uses of previously approved products. The exclusive rights provided to firms that file supplemental NDAs for new uses do not preclude generic competitors from gaining FDA approval to sell the same products for previously approved uses; and once generic versions of these products are available, the FDA has no authority to prevent doctors and pharmacists from substituting the generic version off-label for the branded version sold by the holder of the supplemental NDA. Therefore, the three-year exclusivity provision for supplemental NDAs is likely to have little effect on incentives to conduct clinical trials of new uses of previously approved drugs.

B. FDA as Market Gatekeeper

A far more significant way that the FDA motivates firms to conduct rigorous clinical trials is by demanding data from clinical trials in its market gatekeeper role. The FDA is charged by statute with keeping new drugs off the market pending the submission of the results of “adequate and well-controlled investigations” indicating that they are safe and effective for their intended use.⁵⁵ FDA regulation gives firms powerful incentives to test their products thoroughly enough to satisfy rigorous scientific standards of safety and efficacy for at least one indication. In order to get an NDA approved, a firm must submit “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.”⁵⁶ The statute repeatedly refers to the intended use of the drug in defining the standard for approval, indicating

extended. See Best Pharmaceuticals for Children Act of 2002, Pub. L. No. 107-109, 115 Stat. 1408 (codified as amended in scattered sections of 21 & 42 U.S.C.).

54. 28 U.S.C.A. § 355a (West 2001 & Supp. 2004).

55. 21 U.S.C. § 355(d) (2000).

56. *Id.* § 355(b)(1)(A).

that determinations of safety and efficacy are meaningful only with respect to a particular intended use. It thus directs the Secretary⁵⁷ to reject the NDA if the submitted reports “do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use *under the conditions prescribed, recommended, or suggested in the proposed labeling* thereof,”⁵⁸ if “the results of such tests show that such drug is unsafe for use *under such conditions* or do not show that such drug is safe for use *under such conditions*,”⁵⁹ 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 use prescribed, recommended, or suggested in the proposed labeling* thereof.”⁶⁰ The central role of the particular indication that is being tested carries over into the statutory definition of “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 have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.⁶¹

But once a new drug gets to market, the FDA does not prevent its off-label use for other indications that have never been tested. The FDA does not regulate the practice of medicine, and doctors are free to prescribe approved drugs as they see fit.⁶² This limits significantly the incentives of firms to continue testing their products for new uses once their NDAs have been approved, with a corresponding gap in the quality of data supporting the safety and efficacy of drugs for new uses. For many lucrative drugs, off-label sales account for a significant portion of sales.⁶³

57. The statute confers regulatory authority upon the Secretary of Health and Human Services, although the Secretary turns to FDA to make the necessary judgments.

58. 21 U.S.C. § 355(d)(1) (emphasis added).

59. *Id.* § 355(d)(2) (emphasis added).

60. *Id.* § 355(d)(5) (emphasis added).

61. *Id.* § 355(d) (emphasis added).

62. *See, e.g.,* FTC v. Simeon Mgmt. Corp., 391 F. Supp. 697, 706-07 (N.D. Cal. 1975), *aff'd*, 532 F.2d 708, 717 (9th Cir. 1976). Off-label prescribing of drugs is a significant part of medical practice in some specialties, including oncology. *See* Lars Noah, *Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy*, 28 AM. J.L. & MED. 361, 397-98 (2002).

63. A much-cited example is the drug Gabapentin, approved by the FDA for adjunctive therapy in the treatment of partial seizures and postherpetic neuralgia and prescribed off-label for other indications representing as much as ninety-five percent of sales. *See* Alicia Mack,

Rigorous clinical trials of new uses of previously approved products are not only costly, but can also be extremely risky for a firm that has a lucrative product on the market. A conspicuous example of the risks that rigorous clinical trials pose to a drug manufacturer that is already enjoying brisk off-label sales can be found in the National Institutes of Health (NIH) Women's Health Initiative study on the effects of hormone replacement therapy (HRT) on the risk of heart disease in post-menopausal women.⁶⁴ 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. Even without further FDA approval, this evidence brought about widespread off-label prescription and use of HRT for the purpose of preventing heart disease. HRT manufacturers, although formally prohibited from actively promoting HRT for this 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' and patients' beliefs to more rigorous tests. When NIH (not the manufacturer) finally conducted a long-term, randomized, controlled study involving over 16,000 patients, the results indicated an *increased* risk of heart disease (as well as increased risks of other diseases) in women receiving HRT. This information is undoubtedly valuable to patients, physicians, health insurers, and policy makers, but it sharply reduced sales of Prempro.⁶⁵ In this case, government funding provided valuable and credible information that the product's manufacturer had little incentive to uncover on its own.⁶⁶

Examination of the Evidence for Off-Label Use of Gabapentin, 9 J. MANAGED CARE PHARMACY 559, 559 (2003), <http://www.amcp.org/data/jmcp/Contemporary%20Subject-559-568.pdf>. The manufacturer, Warner-Lambert (now owned by Pfizer) ultimately pled guilty to charges of illegal promotion of the drug for off-label uses and settled the case for \$430 million. See Bernadette Tansey, *Huge Penalty in Drug Fraud: Pfizer Settles Felony Case in Neurontin Off-Label Promotion*, S.F. CHRON., May 14, 2004, at C1.

64. 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).

65. 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, § 1, at 1.

66. One might imagine that health insurers or HMOs would be motivated to conduct clinical trials of drugs to determine their value and to decide whether to pay for them. Insurers presumably have access to patient populations and medical records that place them in a good position to observe the relative benefits and harms of different treatments and they sometimes make such data available for studies. See, e.g., David J. Graham et al., *Risk of Acute Myocardial Infarction and Sudden Cardiac Death in Patients Treated with Cyclo-Oxygenase 2 Selective and Non-Selective Non-Steroidal Anti-Inflammatory Drugs: Nested Case-Control Study*, 365 THE LANCET 475 (2005)

Although the FDA has no authority to prevent prescriptions of approved drugs for off-label uses, it has some statutory authority over the marketing claims that may be made on behalf of such drugs by the manufacturers and has sometimes sought to use this authority to prevent firms from promoting drugs for off-label uses. Firms have resisted this form of regulation, arguing with some success in the courts that it violates their First Amendment rights to disseminate information about their products to physicians.⁶⁷ For example, in *Washington Legal Foundation v. Friedman*,⁶⁸ an industry-supported nonprofit raised 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 distribution of reprints of publications and through manufacturer involvement in continuing medical education programs.⁶⁹ The FDA claimed that distribution of these materials by product manufacturers amounted to unapproved “labeling” that rendered these products “misbranded” in violation of the federal Food, Drug & Cosmetic Act (FDCA). The district court concluded that the regulated activities were commercial speech and put the burden on the FDA to show that the regulation was no more extensive than necessary to advance a substantial government interest.⁷⁰ 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. The court concluded that the first interest was inadequate to justify the intrusion on speech, but that the second interest was substantial.⁷¹ Ultimately, the FDA revised its guidance documents to permit firms to distribute reprints of journal

(basing study on data from Kaiser Permanente). 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. By withholding coverage of off-label prescriptions, they sometimes play a role in demanding such information.

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

68. 13 F. Supp. 2d 51.

69. *See* Draft Policy Statement on Industry-Supported Scientific and Educational Activities, 57 Fed. Reg. 56,412 (Nov. 27, 1992); David G. Adams, *FDA Policy on Industry-Supported Scientific and Educational Activities: Current Developments*, 47 FOOD & DRUG L.J. 629 (1992).

70. 13 F. Supp. 2d at 65, 69-74.

71. 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.

articles regarding off-label uses, effectively permitting some marketing of drugs for unapproved uses without the risk and expense of the sort of trials that are necessary to satisfy the FDA.⁷²

One would expect this change in regulations to diminish the incentives of firms to conduct rigorous clinical trials of previously approved products for new uses. Moreover, the current administration has shown notably less inclination to enforce restrictions on marketing claims against the pharmaceutical industry,⁷³ further minimizing the force of remaining restrictions. Nonetheless, some firms continue to conduct post-marketing studies of approved drugs in the hope of getting supplemental NDAs approving uses for new indications, despite the costs and risks.

Merck's trial of Vioxx for the supplemental indication of preventing recurrence of colon polyps is a striking recent example.⁷⁴ Why would Merck put its revenues from a successful product at risk by conducting such a trial? Extensive media attention to Vioxx in recent months offers a rare glimpse behind the scenes of such decisions.⁷⁵ Presumably Merck hoped to expand the market for Vioxx to include patients at risk of recurring colon polyps, rather than limiting sales to ulcer-prone patients with arthritis and menstrual cramps, and additionally hoped that the post-marketing study would show that the drug was safe and effective for this lucrative new indication. Of course, Merck might have attempted to generate off-label sales for this indication without going to the trouble of conducting the sort of trial that would meet with FDA approval of a supplemental NDA, perhaps by conducting more limited studies and circulating reprints.⁷⁶ However, a prophylactic indication against a relatively low risk might be a hard enough sell for an expensive drug to make the constraints on off-label marketing problematic.⁷⁷ A similar study was already underway for Pfizer's rival

72. Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices, 63 Fed. Reg. 64,556 (Nov. 20, 1998). The revised guidance documents followed explicit Congressional authorization for manufactures to distribute publications that discuss off-label uses as part of the FDA Modernization Act of 1997, Pub. L. No. 105-155, § 401(a), 111 Stat. 2296, 2356-64 (1997) (codified at 21 U.S.C. §360aaa (2000)).

73. See MINORITY STAFF OF HOUSE COMM. ON GOV'T REFORM, 108TH CONG., FDA ENFORCEMENT ACTIONS AGAINST FALSE AND MISLEADING PRESCRIPTION DRUG ADVERTISEMENTS DECLINED IN 2003 (Comm. Print 2004).

74. See *supra* notes 3-9 and accompanying text.

75. See, e.g., Alex Berenson et al., *Despite Warnings, Drug Giant Took Long Path to Vioxx Recall*, N.Y. TIMES, Nov. 14, 2004, at A1; Martinez et al., *supra* note 4; Mathews & Martinez, *supra* note 5.

76. See *supra* note 72 and accompanying text.

77. *Id.*

product Celebrex,⁷⁸ threatening to put Merck at a marketing disadvantage if Celebrex were approved for an indication that remained off-label for Vioxx.

Recent newspaper accounts also suggest that early concerns about the safety of Vioxx may have fortified Merck's resolve to pursue studies of additional indications.⁷⁹ There were indications that Vioxx presented an increased risk of cardiovascular events in data from an early study comparing Vioxx to naproxen,⁸⁰ although Merck took the position at the time that the difference reflected a protective effect of naproxen rather than a toxic effect of Vioxx.⁸¹ Nonetheless, both Merck and the FDA thought the cardiovascular effects of Vioxx called for further study, although they agreed that it would be difficult and ethically problematic to design a clinical trial that would compare Vioxx and a placebo in at-risk patients solely for the purpose of observing side effects.⁸² According to *Wall Street Journal* reporters, Merck marketing executives also opposed a study of cardiovascular risks out of concern that it would signal a lack of confidence in Vioxx.⁸³ Instead, Merck scientists decided, in consultation with the FDA, to await further data on cardiovascular effects of Vioxx from ongoing studies of new indications, signaling optimism about future markets rather than concerns about side effects. Meanwhile, as more data came in, the FDA reached an agreement with Merck to disclose cardiovascular risks in the product labeling in 2002.⁸⁴ Perhaps Merck hoped that rigorous long-term studies, culminating in FDA approval of a supplemental NDA, would put these concerns to rest while expanding the market for its product. Ultimately, of course, that is not what happened. But although the trials were a failure from the perspective of Merck and its shareholders, this episode suggests that the current combination of regulatory carrots and sticks can sometimes motivate firms to undertake very risky investments in clinical trials of their products for new uses.

78. See Scott D. Solomon et al., *Cardiovascular Risk Associated with Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention*, 352 *NEW ENG. J. MED.* 1071, 1072 (2005). The Celebrex trial began enrolling patients in November 1999 and stopped administering the study drug on December 16, 2004 after data analysis revealed increased cardiovascular risks to patients receiving the drug. The similar Vioxx trial began enrolling patients in February 2000 and was terminated on September 30, 2004. See Robert S. Bresalier et al., *supra* note 6.

79. Berenson et al., *supra* note 75.

80. See Claire Bombardier et al., *Comparison of Upper Gastrointestinal Toxicity of Forecoxib and Naproxen in Patients with Rheumatoid Arthritis*, 343 *NEW ENG. J. MED.* 1520 (2000).

81. *Id.* at 1526.

82. Berenson et al., *supra* note 75.

83. *Id.*; see also Mathews, *supra* note 7.

84. See Press Release, FDA, FDA Issues Public Health Advisory on Vioxx as its Manufacturer Voluntarily Withdraws the Product (Sept. 30, 2004), <http://www.fda.gov/bbs/topics/news/2004/NEW01122.html>; see also Mathews & Martinez, *supra* note 5.

III. TRADE SECRECY

From a public policy perspective, the most problematic form of legal protection for data from clinical trials is trade secrecy. Although the pharmaceutical industry has long taken the position that the data from clinical trials of drugs constitute proprietary trade secret information, trade secrecy severely restricts the social value of this information by giving patients and care providers access to only as much of the data as the trial's sponsor chooses to reveal. The FDA has consistently supported this position⁸⁵ and withheld the data from public disclosure as a matter of administrative practice,⁸⁶ although the statutory language invoked in support of this position is ambiguous.⁸⁷ Amendments to the FDCA as part of the Hatch-Waxman Act of 1984 appeared to require that safety and effectiveness data for a drug be made available to the public, "unless extraordinary circumstances are shown," as soon as the periods of data exclusivity have expired and an ANDA "could be made effective if such an

85. Although the FDA does not disclose the underlying data, it requires disclosure of certain information in the labeling of approved products. 21 C.F.R. pt. 201 (2004). 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., Drugs @ FDA, supra* note 23.

86. *See, e.g., 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); 42 Fed. Reg. 3094, 3106 (Jan. 14, 1977) (noting that the FDA has treated data from clinical trials as a trade secret since 1938); 39 Fed. Reg. 44,601, 44,612 (Dec. 24, 1974) ("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.").

87. Proponents of trade secrecy have relied upon section 301(j) of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C.A. § 331(j) (West Supp. 2004), 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 . . . 355 . . . concerning any method or process which as a trade secret is entitled to protection.

Id. 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 by now longstanding administrative practice would make it difficult to adopt a narrower reading of the provision. *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 (1984).

application had been submitted.”⁸⁸ However, so far the industry has successfully resisted a plain meaning interpretation of this provision.⁸⁹

Trade secrecy and FDA regulation are intertwined at a number of levels. At least as a historical matter, an important component of the value of safety and effectiveness data from the perspective of drug manufacturers lay in its utility in overcoming regulatory entry barriers.⁹⁰ The FDCA requires the submission of “full reports”⁹¹ 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 was arguably more substantial prior to the Hatch-Waxman Act than it is today. Under current law, pioneers are substantially protected from generic entry during the statutory periods of data exclusivity by the inability of competitors to use an ANDA during that time.⁹² Moreover, current law directs the FDA to stay the approval of competing products that are covered by patents listed in the *Orange Book* for at least thirty months following a challenge by the patent owner, or until the expiration or successful challenge to the validity of the listed patents.⁹³ It is possible that a generic competitor might use publicly available data to submit its own NDA prior to the end of the data exclusivity period if all 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.⁹⁴ 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 show that its product is bioequivalent to a previously approved product and has no regulatory need to

88. Hatch-Waxman Act, Pub. L. No. 98-417, § 104, 98 Stat. 1597 (1984) (codified as amended at 21 U.S.C. § 355(l) (2000)).

89. 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, at 277-86 (1986).

90. O'Reilly, *supra* note 87.

91. See *supra* note 53 and accompanying text.

92. 21 U.S.C.A. § 355(j)(5)(F)(ii) (West Supp. 2004).

93. *Id.* §§ 355(c)(3), (j)(5)(B). A court before which the patent litigation is pending has some latitude to modify the period of the stay under the terms of the statute. See *supra* notes 39-43 and accompanying text.

94. § 355(l)(5) (West 1999 & Supp. 2004).

replicate the data previously submitted by the holder of the original NDA. 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.⁹⁵

Apart from this much-reduced value to drug manufacturers in overcoming regulatory barriers, data from clinical trials may be valuable to competitors in guiding their own R&D. The data may, for example, alert 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, thereby allowing them to deploy their own R&D resources more efficiently. Trade secrecy permits firms to withhold this value from competitors while exploiting it themselves; however, it does so at 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 and steer them away from carrying out costly trials of products that are likely to fail, thereby perhaps bringing down the staggering average costs of new drug development.⁹⁶ It would also 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 foregone social value of undisclosed data from clinical trials is likely to be a growing loss, as information technology improves and as 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 patients. The FDA is sitting on a treasure trove of data for such purposes.

Public availability of data from clinical trials would also be valuable for patients, doctors, and insurers, permitting them to make better choices of drugs. To the extent that data disclosure is valuable to these customers, one might expect firms to have some motivation to provide it. Indeed, trade secrecy is a tricky strategy for information-rich 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 presumably with some loss of credibility for their claims.

FDA regulation has so far enabled firms to sustain trade secrecy for competitively valuable information while still capturing some of its value to

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

96. See *supra* note 2.

customers. FDA approval, in consultation with panels of outside experts, serves a certification function that enhances the credibility of informational claims about products while preserving the substantial secrecy of the underlying data. FDA regulation combines the bureaucratization of study design and data analysis with a system of scientific peer review and certification of undisclosed data. In the process, it tends to standardize the data that is collected and the format in which summary information is disclosed to the public, clarifying and simplifying the information signals given to a public that is unable to evaluate the data for itself. But the combination of trade secrecy and FDA regulation inevitably leads to suspicion of a regulatory process that is not transparent, especially when previously undisclosed product risks ultimately emerge. Moreover, sequestering valuable data within the FDA limits its social value by constraining access on the part of health care providers who might use it to make better therapeutic choices and by competitors who might use it to develop better products at lower cost.

CONCLUSION

Clinical trials to assess the effects of drugs in patients constitute a valuable form of R&D that offers the prospect of improving decisions about how best to use drugs to prolong and improve human life. But because the results of rigorous trials could potentially reduce product sales rather than increase them, drug-developing firms may not reliably capture the value of this R&D. How to motivate firms to make socially efficient investments in studying the effects of drugs in patients is thus a major challenge for the legal system.

Patent protection, FDA regulation, and trade secrecy each offer firms some protection against the use of data from clinical trials by free riders in competition with them, but each has its limitations, particularly as a mechanism for appropriating the value of information about new uses of old drugs. Trade secrecy offers firms the prospect of suppressing unfavorable information, thereby minimizing the risk to firms that trials of new uses will diminish sales revenues. On the other hand, trade secrecy truncates the social value of the resulting information by sequestering it from the people who stand to benefit from its disclosure and is therefore the most problematic of these legal regimes. More value could be realized overall by combining exclusive rights in product markets with public disclosure of data from clinical trials. This balance of public disclosure with private exclusionary rights is familiar to students of the patent system. Congress appears to have attempted to achieve a similar balance for data from clinical trials in the Hatch-Waxman Act, although regrettably that is not how the FDA has interpreted the legislation. The resulting secrecy limits the information base for making current health care choices and for developing future products, and calls into question the good faith of drug developing firms and the judgment of the FDA. Perhaps it is time to try a more open approach.