

The Role of FDA in Innovation Policy¹

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The history of the US 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 FDA's legal authorities in response to popular pressure for regulation following public health crises,³ and then tightened the agency's leash in response to pressure from industry and

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³ 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 publication of a series of magazine articles exposing fraudulent and dangerous practices by sellers of "patent medicines" and 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 & Cosmetic Act of 1938, which expanded 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 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 & 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 initiative gained a crucial boost to overcome what had previously seemed like insurmountable opposition in the face of public outcry over a recent disaster.

opponents of regulation during periods of ascendancy for free market ideology.⁴ Throughout this period the most politically compelling arguments in favor of regulation have emphasized public health and the protection of patients from unknown hazards, while the most compelling arguments against regulation have emphasized the interests of patients and doctors in making their own therapeutic choices unfettered by government regulation.

Another set of tradeoffs has figured in debates 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 R&D, while 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.⁵ When drug regulation is noted in these debates, it is typically invoked by the patent advocates as a 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, in

⁴ Again, Hilts 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, *id.* at 210-54, and of House Republicans under the leadership of Newt Gingrich in the 1990s, *id.* at 295-331. These efforts have more typically succeeded in curtailing the resources available to FDA than in curtailing its legal authorities, although a notable exception was passage of the Dietary Supplement and Health 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 FDA to regulate dietary supplements, vitamins and herbal remedies sold for therapeutic purposes without testing for safety and efficacy.

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).

⁵See, 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 BROOKLYN J. INT'L L. 363 (2000).

which 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 competing public health goals, by making it costly.

This framing of the relationship between patents and drug regulation 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 poison, today drug regulation guides the development of information that turns poisons, used advisedly, 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 relatively cheap, but determining which molecules are safe and therapeutically effective has remained stubbornly expensive, time-consuming, and risky. Information about drug effects is an extremely valuable resource for guiding doctors, patients, and insurers to make sound therapeutic choices, and for guiding researchers to develop better products in the future. For the most part, we rely on drug-developing firms to produce this information. But we have good reason to worry that in an unregulated market the motivation of firms to supply this information would be less than optimal. 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.⁶ Pharmaceutical firms sell drugs rather than selling information as such, and they thus have an incentive to cheat in developing and selectively disclosing information about their products. Getting firms to provide high quality information about the effects of drugs in patients is thus a major challenge for regulators.

Drug 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 FDA has over the pharmaceutical industry is its premarket approval authority,⁷ which permits FDA to keep new products off the market pending proof of safety and efficacy.⁸ Although premarket approval was originally understood primarily as a consumer protection measure, in the past twenty years Congress has repeatedly fine-tuned FDA's mandate as 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

⁶ Recent examples include revelations about the cardiovascular effects of selective Cox-2 inhibitors (such as 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.

⁷ Federal Food, Drug, and Cosmetic Act § 505, codified as amended at 21 U.S.C. § 355.

⁸ Although generic versions of previously approved products are also considered new drugs, requiring 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 355(b) with 355(j). See *infra* at .

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 the profits from drug development as well as adding to its costs.

Indeed, drug regulation has become an increasingly important source of market exclusivity for innovating firms as the role of the patent system in drug development has become more complex and ambiguous. 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 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 patents may have expired by the time the products are brought to market,⁹ 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. In recent years firms have become quite creative about strategies to secure “evergreening” patents on modified versions of old molecules, but the industry has had limited success in persuading the courts to enforce these patents against generic competitors. 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 from

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 received five years of market exclusivity before FDA would entertain an abbreviated new drug application (ANDA) from a generic competitor. See *infra*.

pharmaceutical end product development. These upstream patents are more likely to add to the costs of drug development than they are to add to its profits.

This paper reexamines the role of FDA regulation in motivating investments in biopharmaceutical innovation. I begin by challenging the standard story that it is the patent system that makes drug development profitable, while drug regulation makes it costly, 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 legislators and from the perspective of firms. In the balance of the paper, I turn to the role of FDA in regulating clinical trials of new drugs, reconsidering its regulatory functions from the perspective of innovation policy rather than from the more conventional perspective of protecting health and safety. Some aspects of the current regulatory scheme make more sense from this revisionist perspective than they do from the conventional perspective, while others come in for new criticisms and suggest new questions for scholars and policy makers.

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.¹⁰

¹⁰ A recent study from the industry-funded Tufts Center for the Study of Drug Development estimates average costs to develop a new drug to be \$802 million, using self-reported data and applying a discount rate of 11% to capitalize average out-of-pocket costs of \$

Biomedical research is a large part of overall R&D in both the public and private sectors, and it is an area in which patents really seem to matter.¹¹ The pharmaceutical industry has long and ardently maintained that patents on drugs are crucial to the financial viability of drug development.

But 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”¹² patents that cover the

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. 151-185 (2003). Critics immediately challenged this estimate as inflating the true costs. See Public 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>> (visited July 29, 2004); 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).

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*, 21 *In Vivo: The Business & Medicine Report* 21:10 (Nov. 2003), <http://www.bain.com/bainweb/PDFs/cms/Marketing/rebuilding_big_pharma.pdf> (visited Jan. 15, 2004). 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.

¹¹ 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. W.M. Cohen et al., *Protecting Their Intellectual Assets: Appropriability Conditions & Why U.S. Manufacturing Firms Patent (Or Not)* (National Bureau of Econ. Research Working Paper No. 7552, 2000); Richard C. Levin et al., *Appropriating the Returns from Industrial Research and Development*, in 3 *BROOKINGS PAPERS ON ECONOMICS ACTIVITY* 783 (Martin N. Baily et al, eds., 1987)..

¹² 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.

drug molecule itself, without limitation as to use. Such patents may be enforced against competitors who make, use, sell or import¹³ the same product for any purpose throughout the patent term. Patents on particular methods of treatment involving the use of a drug have generally been considered less valuable, because they cannot stop competitors from selling the same product for other uses.¹⁴ In theory, the patent holder could still enforce the patent against patients who use the product for the patented use, or against doctors who prescribe it for such use, or against pharmacists who fill the prescriptions, or against manufacturers who urge any of these actors to substitute their bioequivalent product for the patent holder's product in such prescriptions.¹⁵ But these remedies are generally considered less satisfactory than an injunction that will stop the competing manufacturer from making the product entirely.¹⁶

Despite their advantages, from the perspective of the pharmaceutical industry, composition of matter patent protection for new drug products begins and ends too early. This is because 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 standards that put dilatory applicants at risk of losing patent protection

¹³ These acts are defined as direct infringements in 35 U.S.C. § 271(a).

¹⁴ See, e.g., *Allergan v. Alcon Labs., Inc.*, 324 F.3d 1322 (Fed. Cir. 2003).

¹⁵ 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).

¹⁶ This is because 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 users than it is to sue a single manufacturer. Moreover, 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 of America, which has brought infringement actions against individuals who download copyright-protected music.

entirely,¹⁷ making it important to file a patent application on a new composition of matter as soon as one can establish a patentable utility for it, which is typically years before first commercial marketing of a drug.¹⁸ Under current law,¹⁹ patents expire twenty years after their filing dates, 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

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. 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. 35 U.S.C. § 102(g).

¹⁸ 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 FDA to bring a new drug to market. E.g., *In re Brana*, 51 F.3d 1560, (Fed. Cir. 1995) (“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.”).

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).

²⁰ 35 U.S.C. § 154(a)(2). 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. 35 U.S.C. § 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, although the courts may be skeptical of the validity of the later-issued patents. See, e.g., *Geneva v. Glaxosmithkline*, 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”).

pending regulatory approval of a new drug, so long as the total of remaining patent life after extensions does not exceed fourteen years from the date of approval.²¹ 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.²² 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.²³ But sometimes the effective patent life for new drugs is far less than that. For example, the antidepressant drug Paxil did not get to market until after its basic patent had expired.²⁴

²¹ 35 U.S.C. § 156.

²² 35 U.S.C. §§ 156(c), (g)(1)(B), (g)(6).

²³ H.G. Grabowski and J. Vernon, *Effective Patent Life in Pharmaceuticals*, 19 INT’L J. TECH. MGMT 98-120 (2000). Subsequent to the study period, Congress provided for additional six-month extensions for pediatric studies in the FDAMA of 1997.

²⁴ See *SmithKline Beecham v. Apotex*, 365 F.3d 1306 (Fed. Cir. 2004). 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 on February 8, 1977 with 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. 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 at <<http://www.fda.gov/cder/approval/index.htm>> (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, and still in effect on the FDA approval date, and it was this later patent that it selected 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

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, review times at the FDA have been greatly reduced since 1992, when the Prescription Drug User Fee Act brought the agency new resources to hire additional staff to expedite the review process and made these resources contingent upon timely reviews.²⁵ The most recent FDA data 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.²⁶ These periods account for only a small portion of the patent life that ticks away 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.²⁷ This information is an integral part of the value of new drugs, and a

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). 365 F.3d 136 (Fed. Cir. 2004).

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).

²⁵ 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, passed as title 5 of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Pub. L. No. 107-188, §§ 501 et seq. (2002).

²⁶ U.S. FDA, FY 2003 Performance Report to Congress, posted on the internet at <http://www.fda.gov/oc/pdufa/report2003/overview2003.html> (visited Aug 3, 2004).

²⁷ 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 text of

patent term that begins long before this 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 arsenals as old ones expire.²⁸ Examples include patents on “metabolites” of drugs (i.e., the products into which drugs are broken down in a patient’s body);²⁹ patents on intermediate products used in producing drugs;³⁰ patents on new uses of drugs;³¹ and patents on new formulations or preparations of drugs.³² Sometimes innovating firms have succeeded in getting such patents issued by the PTO, and in using the patents to defer FDA approval of generic products for years pending resolution of patent infringement claims.³³ Ultimately, however, their track record in enforcing these infringement claims in the courts has been considerably worse,³⁴ suggesting that the combination

whether the patent term is poorly timed as a source of exclusive rights to motivate drug development.

²⁸ 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); Federal Trade Comm’n, *Generic Drug Entry Prior to Patent Expiration: An FTC Study* (2002).

²⁹ See, e.g., *Schering Corp. v. Geneva*, *Novartis v. Eon Laboratories*

³⁰ See, e.g., *Ben Venue Laboratories v. Novartis Pharmaceutical Corp.*, 10 F. Supp. 2d 446 (D.N.J. 1998).

³¹ See, e.g., *Allergan v. Alcon Laboratories*, 324 F.3d 1322 (Fed. Cir. 2003).

³² See, e.g., *Biovail Corp. v. Andrx Pharmaceuticals, Inc.*, 239 F.3d 1297 (Fed. Cir. 2001).

³³ See, e.g., *Apotex v. Thompson*, 347 F.3d 1335 (Fed. Cir. 2003).

³⁴ See, e.g., *SmithKline Beecham v. Apotex*, 365 F.3d 1306 (Fed. Cir. 2004)(use of drug in clinical trials more than a year prior to filing of patent application on metabolite created statutory bar rendering metabolite patent invalid); *Glaxo Wellcome v. Impax Laboratories*, 356

of patents and FDA regulation is doing more to protect these patent holders from competition than patents could do alone.

Meanwhile, pharmaceutical firms find themselves targeted more often with demands to pay for licenses to use the patented inventions of biotechnology firms and universities. Some biotechnology firms try to stake out market niches somewhere “upstream” from 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 big users of the patent system in the last 25 years, since passage of the Bayh-Dole Act of 1980³⁵ encouraged them to patent the discoveries that they make with federal funds.³⁶ A large

F.3d 1348 (Fed. Cir. 2004)(affirming summary judgment of noninfringement of patent on sustained release formulation of bupropion hydrochloride in favor of generic competitor that used HPC in lieu of HPMC specified in claim); Geneva Pharmaceuticals v. GlaxoSmithKline, 349 F.3d 1372 (2003)(holding invalid on grounds of nonstatutory double patenting subsequently issued patents related to antibiotic on which previously issued patents had expired); Schering v. Geneva, 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 of these 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, 365 F.3d 1306 (Fed. Cir. 2004)(opinion of Rader, J., holding patent invalid under 35 U.S.C. § 102(b)) with *Id.* at (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).

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

³⁶Universities owned 1.1% of U.S. corporate-owned patents issued between 1969 and 1986; by 1999 that number had risen to 4.8%. U.S. Pat. & Trademark Office, *U.S. Colleges and Universities- Utility Patent Grants, Calendar Years 1969-2000*, posted on the USPTO website at

percentage of university patenting activity is in biomedical research,³⁷ and universities have not hesitated to enforce their patents against pharmaceutical firms.³⁸ 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

³⁷See D.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 Research Policy 99, 117 (2001) (noting that leading patents at the University of California, Stanford, and Columbia “are concentrated in the biomedical arena.”); see also Annetine C. Geljins & Samuel O. Thier, *Medical Innovation and Institutional Interdependence: Rethinking University-Industry Connections*, 287 JAMA 72, 75 (2002) (observing that medical center at Columbia accounts for nearly 85% of all licensed inventions). [new book by Mowery, Nelson, Sampat & Ziedonis]

³⁸ 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 claims inhibitors of this enzyme. The university brought patent infringement actions against pharmaceutical companies that made such once lucrative cox-2 inhibitor products as Vioxx and Celebrex. See *University 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). The University of California’s \$200 million settlement with Genentech, M. Barinaga, “Genentech, UC Settle Suit for \$200 Million” *Science* **286**, 1655 (1999), and the University of Minnesota’s \$300 million settlement with Glaxo-Wellcome, University of Minnesota, “Fact Sheet on Glaxo-Wellcome AIDS Discovery Settlement” (Oct. 5, 1999), posted on the internet at <http://www1.umn.edu/urelate/newsservice/newsreleases/99_10glaxofacts.html> (last visited Dec. 16, 2002), 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. M. Fisk, “Ivory towers fire back over patents: More schools are suing businesses” *National Law Journal* **24**:49, A1 (Aug. 26 2002).

databases, newly identified (or characterized) drug targets, genetically engineered animal models, and new laboratory techniques, instruments, and reagents. These "upstream" inventions that 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.³⁹ From the perspective of a drug-developing firm, they are so many syphons at the feeding trough of the next pharmaceutical blockbuster, draining away profits in many different directions.

In sum, although the unequivocal 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 be counted upon to secure effective market exclusivity for drug developing firms beyond that provided by the FDA.

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 an entry barrier 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 solely to protect health

³⁹ Rebecca S. Eisenberg, *Bargaining Over the Transfer of Proprietary Research Tools: Is This Market Failing or Emerging?*, in R. Dreyfuss et al. eds., *Expanding the Boundaries of Intellectual Property: Innovation Policy for the Knowledge Society* (Oxford 2001).

and safety, but rather 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 piece of U.S. legislation in this regard was the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the “Hatch-Waxman Act.”⁴⁰ 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 off patent. 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.⁴¹ At the same time, FDA treated clinical trial data submitted to the agency by pioneer firms as proprietary information belonging to the submitter that the agency would not disclose or permit others to rely upon.⁴² Generic drug companies could not conduct their own clinical trials until after patents on the drugs expired without exposing themselves to infringement liability.⁴³ Even after patent expiration, generic firms faced prohibitive regulatory costs that they could not recoup in low-margin, competitive markets for off-patent drugs. Generic firms argued that the

⁴⁰ P.L. 98-417, 98 Stat. 1585 (codified as amended at 15 U.S.C. §§ 68g-68d, 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: J.L. & TECH. 389 (1999).

⁴¹ U.S. Food & Drug Admin., *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 and sources cited therein (1996). A limited exception permitted the introduction of generic versions of products that had been on the market since before 1962 on the basis of an abbreviated application.

⁴² 39 Fed. Reg. 44,602 (1974).

⁴³ *Roche v. Bolar*, 733 F.2d 858 (Fed. Cir. 1984).

regulatory entry barrier had to be lowered for generic products in order to bring about price competition in the market for off-patent drugs.⁴⁴ 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.⁴⁵

Congress responded to these divergent criticisms of the status quo with a package of measures that blur 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, or ANDA,⁴⁶ and permitted the necessary clinical trials to proceed during the patent term without infringement liability.⁴⁷ 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 review period prior to the first permitted commercial marketing of a new drug.⁴⁸ At the same time, it set up a complex system for keeping

⁴⁴ 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 , at 396-97. The Hatch-Waxman Act provided for continued use of paper NDAs in a provision codified at 21 U.S.C. § 355(b)(2).

⁴⁵ 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).

⁴⁶ Federal Food, Drug, & Cosmetic Act § 505(j), 21 U.S.C. § 355(j).

⁴⁷ 35 U.S.C. § 271(e).

⁴⁸ 35 U.S.C. § 156. See *supra* note .

track of patents that cover FDA-approved drugs and directed FDA to defer regulatory approval of generic versions of those drugs until after patent expiration.⁴⁹ 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, but if the patent owner files an infringement action within 45 days, 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).⁵⁰ In effect, this 30-month stay of regulatory approval is like a preliminary injunction in favor of a patent holder, administered by the FDA rather than by a trial court, and with no requirement to show likelihood of success on the merits.⁵¹

⁴⁹ 21 U.S.C. §§ 355(b),(c),(j).

⁵⁰ 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 be expansive in listing the 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 Federal Trade Commission, *Generic Drug Entry Prior to Patent Expiration: An FTC Study* (July 2002) <<http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf>> [hereinafter FTC Study]. For a particularly egregious example of this strategy, see *Apotex v. Thompson*, 347 F.3d 1335 (Fed. Cir. 2003)(holding that Hatch-Waxman Act does not require FDA to review patents for validity and infringement before listing them).

⁵¹ In 2002 the Bush administration announced a plan to limit patent holders to a single 30-month stay per product by FDA rule, without new legislation. See Dep't. of Health & Human Services, Food & Drug Administration, *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*, <http://www.fda.gov/OHRMS/DOCKETS/98fr/PATENT.pdf>. The FTC previously proposed such a rule. FTC Study at ii. According to recent Congressional testimony of Lester

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. 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, PTO is called upon to look at 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.

FDA-Administered Pseudo-patents

Other legislative initiatives have cast FDA in the role of administering pharmaceutical pseudo-patents, unabashedly directing 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 is the Orphan Drug Act of 1983,⁵² which directs the agency to grant seven years of market exclusivity for products to treat rare diseases and conditions affecting fewer than 200,000

Crawford, 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. See Statement of Lester M. Crawford before the Subcomm. on Health, House Comm. on Energy & Commerce (Oct. 9, 2002), at http://www.fda.gov/ola/2002/hatch_waxman_1009.html. The final rule is set forth at 68 Fed. Reg. 36676 (June 18, 2003).

The limitation to a single 30-month stay was 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).

⁵² P.L. 97-414, 96 Stat. 2049 (1983).

patients in the U.S.⁵³ Although one might expect that products qualifying for this protection would have markets 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.⁵⁴ The effect of FDA-administered market exclusivity under the Orphan Drug Act is similar to the effect of a patent.⁵⁵

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 FDA,⁵⁶ and three years of exclusivity for making changes in a previously approved product that required conducting new clinical trials to win FDA approval.⁵⁷ In contrast to the Orphan Drug Act provisions, these Hatch-Waxman Act exclusivity provisions merely prevent FDA from allowing competitors to obtain streamlined review of their applications without having to submit a full NDA. They do not prevent a competitor from

⁵³ 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).

⁵⁴ "Off-label" use of a drug means use for a purpose other than that for which FDA has approved the drug as safe and effective.

⁵⁵ 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. [cite to cases]

⁵⁶ 21 U.S.C. § 355(j)(5)(F)(ii).

⁵⁷ 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 new indications, or conducts clinical trials to determine whether a drug may safely be switched from prescription to OTC status.

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 with or 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.⁵⁸ The three-year period of data exclusivity for making product changes that require clinical trials to gain approval begins with the approval of the change, 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. 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 old version of the product.

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.⁵⁹ 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, FDA can do nothing

⁵⁸ See *supra* note and accompanying text (discussing Paxil).

⁵⁹ *Bristol-Myers Squibb v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996).

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.

The Food and Drug Administration Modernization Act of 1997⁶⁰ added a provision for 6 months of exclusivity as a reward for conducting pediatric trials of drugs.⁶¹ 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 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 innovation by granting

⁶⁰ P.L. 105-115, 111 Stat. 2296 (1997). 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.).

⁶¹ 28 U.S.C. §355a.

valuable exclusionary rights.⁶²

Another important role played by FDA in supplementing the exclusivity provided by patents is in protecting patent holders against parallel imports of drugs that they have sold at a lower price in another country. Drugs are more expensive in the U.S. than they are anywhere else in the world, as has been much remarked in the popular press.⁶³ This leaves the profits of drug developing firms from sales in the U.S. potentially vulnerable to erosion through arbitrage that moves drugs from low-price to high-price markets.⁶⁴

The legal status of this sort of 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. This doctrine plainly permits buyers to

⁶² Another controversial Hatch-Waxman Act provision that has the effect of using 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 at 57-63. Designed to spur generic competition with products covered by questionable patents, 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. FTC challenged this strategy under the antitrust laws, *id.* at 1-2, and Congress recently moved to curtail these strategies as part of the Medicare prescription drug legislation by defining certain "forfeiture events" that would cause the first generic applicant to lose its right to generic exclusivity. Pub. L. 108-198, approved 12/19/03, 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.

⁶³ See Hal R. Varian, *Examining Differences in Drug Prices*, The New York Times (Sept. 21 2000).

⁶⁴ See C.E. Barfield and M.A. Groombridge, *Parallel Trade in the Pharmaceutical Industry: Implications for Innovation, Consumer Welfare, and Health Policy*, 10 Fordham I.P., Media & Ent. L.J. 185 (1999).

resell in the U.S. secondary market goods (such as used cars) that were purchased in the U.S. 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 to resell them in the U.S.

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 anywhere in the world without needing further permission. This issue has generated considerable debate in trade negotiations, but so far no agreement, leaving each nation free to choose its own exhaustion rule.⁶⁵

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. But it is not entirely clear that this is the law in the U.S.⁶⁶ The U.S. Court of Appeals for the Federal Circuit once observed in passing, with no acknowledgment of controversy, that under U.S. patent law

⁶⁵ Agreement on Trade Related Aspects of Intellectual Property Rights, April 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, Legal Instruments-Results of the Uruguay Round vol. 31, 33 International Legal Materials 81 (1994) <http://www.wto.org/english/tratop_e/trips_e/t_agm0_e.htm> (hereinafter "TRIPS Agreement"), Art. 28, Sec. 1(a), and Art. 6.

⁶⁶ For a careful analysis of this question prior to the Federal Circuit's decision in the *Jazz Photo* case, *infra*, see Margreth Barrett, *The United States' Doctrine of Exhaustion: Parallel Imports of Patented Goods*, 27 N. Ky. L. Rev. 911 (2000).

the first sale doctrine only applies if there has been a sale in the U.S.⁶⁷ But the U.S. Supreme Court has arguably held otherwise in the copyright context, at least if the goods were manufactured in the U.S.,⁶⁸ 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.⁶⁹

Despite the uncertain coverage of U.S. patent law, drug 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.⁷⁰ But the pharmaceutical industry does not rely on these regulatory differences to protect it from parallel trade in drugs in the U.S. 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.⁷¹ There is a genuine

⁶⁷ *Jazz Photo Corp. v. International Trade Com'n*, 264 F.3d 1094 (Fed. Cir. 2001) ("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.).

⁶⁸ *Quality King Distributors v. L'anza Research International*, 523 U.S. 135 (1998).

⁶⁹ *K Mart v. Cartier*, 486 U.S. 281 (1988).

⁷⁰ FDA approval to market a new drug is typically contingent upon the inclusion of specified information in the accompanying label about indications, dosage, side effects, etc. Indeed, 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.

⁷¹ P.L. 100-293, 102 Stat. 95 (codified as amended at 21 U.S.C. §§ 301, 331, 333, 353, 381, & 801(d)).

health and safety issue lurking behind these provisions,⁷² but they also have an economic side effect—preserving the viability of price discrimination across national markets for drugs—that may be even more important. 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,⁷³ and as libertarians have argued that markets should be permitted to equalize the prices charged for drugs in different countries.⁷⁴ Meanwhile, the federal government, invoking health and safety concerns, has taken the lead in prosecuting reimporters of drugs from Canada,⁷⁵ 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 and conducting further clinical trials of previously approved products.

⁷² See FDA Press Release, *FDA/U.S. Customs Import Blitz Exams Reveal Hundreds of Potentially Dangerous Imported Drug Shipments* (Sept. 29, 2003), posted on the FDA website at <http://www.fda.gov/bbs/topics/NEWS/2003/NEW00948.html> (visited Sept. 30, 2003).

⁷³ The ultimate political resolution of this issue remains uncertain. See Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Title XI, Subtitle C - Importation of Prescription Drugs.

⁷⁴ See Roger Pilon, *Drug Reimportation: The Free Market Solution* (Cato Institute 2004), at <http://www.cato.org/pubs/pas/pa521.pdf> (visited April 11, 2005).

⁷⁵ See, e.g., *U.S. v. Rx Depot, Inc.*, 2003 U.S. Dist. LEXIS 20135 (N.D. OK 2003);

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 FDA in protecting public health.⁷⁶ 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,⁷⁷ biotechnology process patent provisions,⁷⁸ and prior user rights for business method patents.⁷⁹ Often the result of legislative compromise after a change proposed by one industry meets opposition from another, these

⁷⁶ The unease of FDA in this relatively new role is perhaps reflected in its reticence to evaluate whether patents designated by pharmaceutical firms for listing in the Orange Book are appropriately listed or not, and 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. [cites]

⁷⁷ 35 U.S.Code § 156.

⁷⁸ 35 U.S. Code § 103(b).

⁷⁹ 35 U.S. Code § 273.

provisions are awkward and cumbersome, and often ill-considered.

Industry-specific patent provisions may also place the U.S. 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.”⁸⁰ This 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 elimination of provisions in national laws of member states that previously weakened drug patents (such as compulsory licensing provisions).⁸¹ But the treaty language is written in broader terms that seem also to prohibit discrimination in favor of drug patents.

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 than 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, at some point 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. But it might be easier to finesse the issue if the protection arises through drug regulation, particularly if the underlying legislation serves a significant non-IP interest such as the protection of health and safety.

⁸⁰ TRIPS Agreement, Art. 27 (emphasis added).

⁸¹ 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).

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

First, FDA provides product market exclusivity, while the patent system provides invention exclusivity. Strengthening patent protection is therefore a two-edged sword for innovating firms. It not only fortifies the drug patents that provide product market exclusivity, but also fortifies patents on the many proprietary inputs into drug development, thus adding to costs as well as revenues for drug-developing firms. FDA-administered exclusivities, by contrast, enhance product revenues without increasing these costs. Second, 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 make these rules 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 the FDA-administered measures that currently support high drug prices than it is to sustain the rights conferred by the patent system. Even the Bush administration, which has enjoyed strong support from the pharmaceutical industry and has been extraordinarily 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.⁸² This change in policy was initially a result of executive action alone, without the need for new legislation, although Congress promptly followed by codifying the new restrictions as part of the Medicare Prescription Drug Improvement and Modernization Act of 2003.⁸³

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 be less durable than those conferred by patents.

FDA Control of Clinical Trials as Innovation Policy

More central to the health and safety mission of FDA than the various provisions for securing market exclusivity to drug developers are (1) its role in approving (or disapproving) the marketing of new drugs⁸⁴ based on clinical evidence of safety and efficacy⁸⁵ and (2) its role in limiting promotional claims that manufacturers make about products under its authority to protect the public from products that are “misbranded.”⁸⁶ Even in these core roles, the agency’s

⁸² See Dep’t. of Health & Human Services, Food & Drug Administration, “Applications for FDA Approval to Market a New Drug: Patent Submission and 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” (June 12, 2003), available on the internet at <<http://www.fda.gov/OHRMS/DOCKETS/98fr/02N-0417-nfr00001.pdf>>. The FTC previously proposed such a rule. FTC Study at ii.

⁸³ Pub. L. No. 108-173 § 1101, 117 Stat. 2071 2448-57, codified at 21 U.S.C. § 355(j)

⁸⁴ FDCA § 505(a).

⁸⁵ FDCA § 505(b).

⁸⁶ FDCA §§ 301, 502.

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. 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 technocratic vernacular of scientific peer review to characterize the standards themselves (“adequate and well-controlled investigations ... by experts qualified by scientific training and experience”).⁸⁷

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

⁸⁷ More specifically, FDCA § 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 ...”

Justifications for FDA's roles as market gatekeeper and censor of promotional claims that focus on the protection of patients from harm invite the objection that patients may be harmed by disease as well as by drugs, and 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 risks from investigational drugs that did not have FDA approval than allow their illnesses to progress pending the results of definitive clinical trials.⁸⁸ 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.

Moreover, this protective approach toward the risks posed by drugs seems anomalous when patients enjoy relatively unfettered access to products like Ephedra.⁸⁹ From a consumer protection 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, while allowing Whole Foods Markets to sell substantially untested and unregulated "dietary supplements" that purport to have similar effects and pose unknown hazards. Of course, one might argue that the way to correct the asymmetry is to eliminate the exemptions that currently allow these dietary supplements and nutraceuticals to remain on the market. But plainly some

⁸⁸ See Steven Epstein, *Impure Science: AIDS, Activism, and the Politics of Knowledge*.

⁸⁹ Although FDA recently announced plans to prohibit sales of products containing ephedra, see FDA Consumer Alert: FDA Plans Regulation Prohibiting Sale of Ephedra-Containing Dietary Supplements and Advises Consumers to Stop Using These Products (Dec. 30, 2003), posted at <<http://www.fda.gov/oc/initiatives/ephedra/december2003/advisory.html>> (visited January 15, 2004), the legal obstacles to banning dietary supplements place a strong burden on the agency and stand in striking contrast to the requirement that manufacturers demonstrate safety and efficacy in order to obtain approval to sell new pharmaceutical products.

consumers (including some members of Congress) want these products and do not want 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.⁹⁰ 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 on safety and consumer protection.

Another anomalous aspect of the current regulatory regime from a consumer protection perspective is FDA's approach to off-label use of products that have been approved only for a narrow set of indications that have been adequately tested. Once a product has been approved for a single indication in a particular group of patients, physicians are free to prescribe it for any patient for any indication, notwithstanding the absence of clinical trials to establish the safety and efficacy of the drug beyond the approved use.⁹¹ Off-label prescription of drugs is a significant part of medical practice in some specialties, notably including oncology. Yet FDA sharply curtails (insofar as the courts will permit)⁹² manufacturers' efforts to disseminate information about off-label uses of drugs to physicians. If off-label uses of drugs threaten patient safety, then from a health and safety perspective it is puzzling that they should be permitted at all. If they do not threaten patient safety enough to prohibit them, then it is puzzling

⁹⁰ E.g., Dietary Supplement Health and Education Act, Pub. L. No. 103-417, 108 Stat. 4325 (1994) (limiting FDA's power to regulate dietary supplements as either food additives or new drugs).

⁹¹ See, e.g., *FTC v. Simeon Management Corp.*, 391 F. Supp. 697, 705-07 (N.D. Cal. 1975), *aff'd* 532 F.2d 708, 717 (9th Cir. 1976).

⁹² The courts in recent years have invalidated regulatory and statutory restrictions on the promotion of pharmaceutical products on First Amendment grounds. See *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998); *Washington Legal Foundation v. Henney*; *Thompson v. Western States Medical Center* (U.S.S.Ct. 2002).

that the law should prohibit rather than promote dissemination to physicians of whatever information is available about these uses to help them 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. FDA uses its powers as market gatekeeper and censor of marketing claims not just to protect patients from untoward risks of harm, but also to motivate drug sponsors to conduct scientifically sound clinical trials that generate valuable information about drugs. These trials are costly, time-consuming, and risky. The information that they provide is valuable, but trial sponsors are unable to capture much of that value, and may in fact stand to lose revenue if the 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.⁹³ How to motivate firms to invest in generating this information in an honest, credible fashion is a major challenge for the law. 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. By requiring that firms conduct rigorous clinical trials before bringing their products to market and before making promotional claims for their products, FDA plays an important structural role in promoting a valuable form of biomedical

⁹³ A very recent case in point is Vioxx, a product that had been approved by 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 colon polyps. See Rebecca S. Eisenberg, *Learning the Value of Drugs—Is Rofecoxib a Regulatory Success Story?* 352 *New England J. Med.* 1285 (2005).

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, FDA preserves public confidence in the integrity of the results while preserving them as proprietary information of the sponsor.

The control mechanisms that 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 their doctors of preliminary information about new uses for drugs that are already on the market, 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 FDA is more likely to be held accountable for harms that result from erroneous approval of a product that proves harmful 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.⁹⁴ Another explanation is that restricting the sale and marketing of drugs serves a distinct interest in getting firms to generate scientifically sound information about the effects of the drug that 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 and making promotional claims for their products, deferring approval until the science is done may be the most effective way of promoting this interest.

⁹⁴ Cite to Mary Olson.

FDA advanced this argument explicitly in support of its restrictions on promotion of off-label use, along with the more standard argument about protecting patients from health risks, in the case of *Washington Legal Foundation v. Friedman*.⁹⁵ 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 distribution of reprints of publications and through manufacturer involvement in continuing medical education programs. 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 and Cosmetic Act. The district court concluded that the regulated activities amounted to commercial speech and put the burden on FDA to show that the regulation was no more extensive than necessary to advance a substantial government interest.⁹⁶ 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 FDA for approval. 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.⁹⁷

⁹⁵13 F. Supp. 2d 51 (D.D.C. 1998).

⁹⁶Central Hudson

⁹⁷ 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.

For purposes of this analysis, what is interesting about this case is (1) that the agency candidly advanced the argument for FDA regulation as a means of promoting investment in clinical trials, and (2) that the court found this interest a more persuasive justification for the regulation than the standard argument for FDA regulation as a means of protecting patients from risks. This framing of the issue in litigation is itself evidence that FDA regulation has moved beyond its traditional patient-protection function towards a more self-conscious goal of promoting certain kinds of R&D.

What Difference Does It Make?

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? Given that the information to be generated in clinical trials of drugs concerns safety and efficacy, perhaps for many purposes the two goals effectively converge. Ultimately, the reason for promoting the particular types of R&D that FDA regulation advances is not simply that we value research and innovation in their own right, but that we value public health and safety and believe that sound clinical trials of new products will advance our health and safety goals. Indeed, one could say the same thing about government involvement in biomedical research more generally. The budget of the National Institutes of Health has grown during times when the budgets of other science agencies have languished because health-related innovation enjoys broader political appeal than other scientific pursuits. This relative political appeal reflects the perceived importance of public health, and the success of the biomedical research community in persuading Congress that government investments in promoting 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.

In addition to explaining some otherwise anomalous features of the current regulatory scheme, this understanding of the function of FDA regulation suggests a number of further questions about how best to 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.

1. The Trigger for Approval. One significant area of potential divergence concerns the appropriate requirements for new product approvals. The current requirement of demonstrating safety and efficacy prior to market 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 generation of scientifically sound information, with the mechanism of premarket approval serving merely to exploit the greater leverage that FDA holds over drug developers at this stage, perhaps 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 suggestion invites a number of objections that highlight the complex role played by 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 toxicities 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, which makes FDA certification 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 might be substituted.

Some critics of 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 products⁹⁸ (or, less optimistically, much as Arthur Andersen certified the accuracy of Enron's financial records). The recent accounting scandals highlight problems with relying on private experts to certify the quality of information generated by their clients. The firms that are likely to have the most pertinent expertise (e.g., firms that currently specialize in designing and conducting clinical trials

⁹⁸ E.g., Henry I. Miller, *To America's Health: A Proposal to Reform the Food and Drug Administration* (Hoover Institution Press 2000).

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 science-based 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 current credibility.

2. *Data Disclosure.* A related issue 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 the data from clinical trials of drugs constitute trade secret information belonging to the firm that submits the data, and FDA has consistently supported this position⁹⁹ and withheld the data from public disclosure as a matter of administrative practice,¹⁰⁰ although the statutory language invoked in support of this position is

⁹⁹ Although FDA does not disclose the underlying data, it requires disclosure of certain information in the labeling of approved products. Moreover, in recent years FDA has begun putting more information about approved products up on its website, including analyses of the data from clinical trials by FDA staff. For example, information about Vioxx is posted at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_Ap provalHistory#apphist> (visited Feb. 21, 1995).

¹⁰⁰ See, e.g., 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.”); 42 Fed. Reg. 3094, 3106 (Jan. 14, 1977) (noting that 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); *Public Citizen Health Research Group v. FDA*, 997 F. Supp. 56 (D.D.C. 1998).

ambiguous.¹⁰¹ Amendments to the Food, Drug, & Cosmetic Act 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 application had been submitted,”¹⁰² but so far industry has successfully resisted a plain meaning interpretation of this provision.¹⁰³

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.¹⁰⁴ The FDCA requires the submission of “full reports”¹⁰⁵ of clinical trials to comply with the requirements for an NDA, which has long been understood to require submission of the

¹⁰¹ Proponents of trade secrecy have relied upon § 301(j) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 331(j), 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.”

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); Note, *FDA Disclosure of Safety and Efficacy Data: The Scope of Section 301(j)*, 52 Fordham L. Rev. 1280 (1983-84).

¹⁰² Section 104 of the Hatch-Waxman Act, 98 Stat. 1597 (1984), codified as amended at 21 U.S.C. § 355(l)..

¹⁰³ See Jane A. Fisher, *Disclosure of Safety and Effectiveness Data under the Drug Price Competition and Patent Term Restoration Act*, 41 Food Drug Cosmetic L. J. 268 (1986).

¹⁰⁴ O’Reilly, *supra* note 84.

¹⁰⁵ See *supra* note 53 and accompanying text.

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 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 protected from generic entry through use of an ANDA during the statutory periods of data exclusivity.¹⁰⁶ Moreover, current law directs 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.¹⁰⁷ 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.¹⁰⁸ 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 replicate the data previously submitted by the holder of the

¹⁰⁶ 21 U.S.C. § 355(j)(5)(F)(ii).

¹⁰⁷ 21 U.S.C. §§ 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.

¹⁰⁸ 21 U.S.C. § 355(l)(5).

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.¹⁰⁹

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. Trade secrecy permits firms to withhold this value from competitors, while exploiting it themselves. But 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.¹¹⁰ 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 foregone social value as a result of secrecy 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 patient populations. FDA is sitting on a treasure trove of data for such purposes.

¹⁰⁹ It is possible that the data could be used to secure regulatory approval to sell generic products in foreign markets.

¹¹⁰ See *supra* note 2 and sources cited therein.

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 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.¹¹¹ 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 signals 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 FDA in evaluating the safety and efficacy of the product. 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

¹¹¹ Consider whether the market for drugs may fail to register effective demand for product information.

analyses by FDA staff, and correspondence,¹¹² 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-makers. In the case of a product that is available by prescription only, the disclosure in the labeling must be provided to prescribing physicians, and in the case of an OTC product, it must be provided to patients and written in terms that are meaningful to them. The sponsor of the clinical trials, or the doctors and scientists participating in its trials, might make further disclosures through publications or press releases, but they typically do not choose to disclose the raw data.

From a patient protection perspective, this approach is probably justifiable, although it might 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, most patients lack the expertise and inclination to review even the limited information about drugs that is currently made available. Doctors, although more expert than patients, are busy people who suffer from information overload and probably get more information than they care to absorb about new drugs from representatives of pharmaceutical firms. Health insurance payors who are concerned about the rising costs of new drugs might in theory have the capacity and incentive to peruse data from clinical trials in order to determine when they should cover the cost of drugs for particular patients, but in practice they depend heavily on prescribing physicians to make these calls for them on a case-by-case basis. The provision of summary

¹¹² See Press Release, FDA Launches New Easy-to-Use Drug Information Web Site (Mar. 3, 2004), posted at <<http://www.fda.gov/bbs/topics/NEWS/2004/NEW01031.html>> (visited March 8, 2004).

information in the product label may well be all that these information users want.

But from other perspectives, this approach is puzzling. 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. Public disclosure would subject to scrutiny the basis for regulatory decisions, helping to ensure that they are well-grounded scientifically. Public disclosure would also 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. The loss from secrecy is a growing loss 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 any given study that is limited to a few thousand patients. Although for some purposes studies of a single drug provide the only meaningful information, some toxic reactions are thought to result from variability across patients in drug metabolism enzymes that are likely to give some patients similar problems with multiple drugs. Such effects might be easier to observe by looking at results from multiple studies, particularly as the field of pharmacogenomics advances.

Although assurances of confidentiality for submitted data are not uncommon in the context of health and safety regulation,¹¹³ government initiatives to promote innovation often call

¹¹³ See *Ruckelshaus v. Monsanto*, 467 U.S. 986 (1984); Thomas O. McGarity & Sidney A. Shapiro, *The Trade Secret Status of Health and Safety Testing Information: Reforming*

for eventual disclosure of new data. The patent system provides for full disclosure of patent specifications,¹¹⁴ 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.¹¹⁵ Sponsored research programs also sometimes call for public disclosure of data, although such requirements may face resistance from investigators with an interest in restrict 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.¹¹⁶ 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.

3. *What Information?* Focusing on FDA regulation as a means of motivating the generation of information highlights the question of what information the system should aim to generate. This is an important question whether the function of regulation is understood from a patient protection perspective or from an innovation incentives perspective. The proper design of clinical trials depends on what questions one asks as well as on what sorts of data one counts

Agency Disclosure Policies, 93 HARV. L. REV. 837 (1980).

¹¹⁴35 U.S.C. § 112.

¹¹⁵ [cites]

¹¹⁶ Final NIH Statement on Data Sharing (Feb. 26, 2003), posted at <<http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html>> (visited March 8, 2004).

as responsive to those questions. In recent years FDA has moved from seeking the submission of data from a homogenous population of subjects that permit isolation of drug effects from other variables to seeking messier but more clinically relevant data from a diverse set of patients, including women and minorities, that might offer a better preview of how future patients will react to the drug. This shift in approach may well be justified if the goal is to provide information that is useful to doctors, but it is not obvious that the information preferences of doctors should dominate regulatory requirements.

The fact that drugs are typically prescribed by doctors and paid for by health insurers complicates the analysis. In recent years pharmaceutical firms have increasingly advertised their products directly to patients, to the dismay of those who believe most patient consumers lack the expertise to evaluate information about drugs themselves. Information dissemination by private firms is driven by profit considerations. The products that firms find it worthwhile to advertise are typically relatively new drugs that are still under patent, available by prescription only, and covered by health insurance. As the ads suggest, patients ask their doctors to prescribe particular products for them. 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 exercise and follow through on 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. But 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 significant limits to the impact of information disclosures that are targeted toward persons involved in the delivery of clinical care.

From an innovation perspective, the more significant users and scrutinizers of information about the clinical effects of drugs may be competing firms that are looking for opportunities to develop superior products or to differentiate their products from others. Competitors with access to information about drug effects might also be motivated to reanalyze the data in order to correct any misleading spin that has been disseminated by the sponsor.

The current system does a better job of testing short-term effects than long-term effects, 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 than it is to get them to continue testing products after they are on the market. The 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 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. From the perspective of innovation policy, as opposed to prophylactic consumer protection, we might rather see more resources invested in post-marketing studies, perhaps conducted under FDA supervision after a product is brought to market, instead of requiring definitive clinical test results before a product may be sold. In recent years FDA has begun moving in the direction of approving the sale of new products under “fast-track” procedures while post-marketing 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 1997.¹¹⁷ But sponsor compliance with these post-marketing requirements has been poor, revealing a serious pragmatic constraint.

One reason for this poor rate of compliance may be that once a product is on the market, it is risky to test it further in long-term trials. A conspicuous recent example of the risks that rigorous clinical trials pose to a drug manufacturer can be found in 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.¹¹⁸ Although 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, and this evidence was good enough to bring about widespread off-label prescription and use of HRT for the purpose of reducing this risk. HRT manufacturers, although formally prohibited from actively promoting HRT for the purpose of reducing the risk of heart disease, 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 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 has sharply reduced sales of Prempro.¹¹⁹ In this case,

¹¹⁷ Codified in pertinent part at 21 U.S.C. § 356.

¹¹⁸ 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," JAMA 288(3):321-33 (July 17, 2002).

¹¹⁹ 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

government funding provided valuable and credible information that the product's manufacturer had little incentive to uncover on its own.¹²⁰

Sometimes firms conduct post-marketing studies of approved drugs in the hope of getting supplemental NDAs approving use for new indications, despite the costs and risks. A striking recent example is Merck's trial of Vioxx, a product that had been approved by FDA for treatment of pain and inflammation associated with osteoarthritis, menstruation, and rheumatoid arthritis,¹²¹ for the supplemental indication of preventing recurrence of colonic polyps.¹²² Vioxx sales were generating sales of \$2.5 billion per year before Merck took it off the market after observing cardiovascular side effects in the course of these post-marketing studies.¹²³ 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

following the announcement of the study results. G. Kolata et al., *Menopause Without Pills: Rethinking Hot Flashes*, The New York Times, Nov. 10, 2002, at A1.

¹²⁰ 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. 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. So far as I can tell, insurers do not currently play a significant role in generating or demanding information about drug effects, although in theory they could step forward to fill this role in a less extensively regulated environment.

¹²¹ See U.S. FDA Center for Drug Evaluation and Research, Vioxx (rofecoxib), posted at <http://www.fda.gov/cder/drug/infopage/vioxx/default.htm> (visited Feb 20, 2005).

¹²² See *supra* notes 3-4 and accompanying text.

¹²³ See Barbara Martinez et al., *Merck Pulls Vioxx From Market After Link to Heart Problems*, Wall St. J., Oct. 1, 2004, at A1.

scenes of such decisions,¹²⁴ revealing that marketing considerations and FDA oversight both played significant roles. Although Merck might have tried to expand the market for Vioxx to include patients at risk of recurring colon polyps through off-label sales, FDA constraints on off-label marketing might have made it difficult to get doctors to adopt an expensive drug for a prophylactic indication against a relatively small risk. Moreover, a similar study was already underway for Pfizer's rival product Celebrex, threatening to put Merck at a marketing disadvantage if Celebrex were approved for an indication that remained off-label for Vioxx.. Early concerns about the safety of Vioxx also played a role. Data from an early study comparing Vioxx to naproxen suggested an increased risk of cardiovascular events for the patients receiving Vioxx. Although Merck took the optimistic position at the time that the difference reflected a protective effect of naproxen rather than a toxic effect of Vioxx, both Merck and FDA thought the cardiovascular effects of Vioxx called for further study. Merck marketing executives were reluctant to do 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. Some recent observers have criticized FDA and Merck for failing to pursue a study focused directly on cardiovascular effects, but such a study would have been less informative than a study that tests efficacy as well as safety. (Indeed, the study revealed that Vioxx is effective in preventing recurrence of colonic polyps.) Information about the side effects of a drug is only meaningful in the context of information about its therapeutic benefits. The fact that Merck undertook such a long-term post-marketing

¹²⁴ See, e.g., Alex Berenson et al., *Despite Warnings, Drug Giant Took Long Path to Vioxx Recall*, New York Times (Nov. 14, 2004)(available at www.nytimes.com); Martinez, *supra* note 4; Mathews, *supra* note 6.

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.

A significant limitation of the current system is that it only works to generate information about products that the manufacturer can sell at a price that permits recovery of the investment, which usually means a drug 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.¹²⁵ The provisions in the Hatch-Waxman Act for additional years of exclusivity before a generic competitor may enter the market through use of an ANDA (as opposed to a costlier NDA) are an effort to limit this sort of free-riding on costly data for products that are no longer under patent. One could expand this approach to promote testing of other unpatented products. 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. Even if generic competitors are forced to duplicate successful clinical trials at their own expense before they can bring their products to market, they incur this cost at less risk than their predecessors faced, knowing that the outcome will be favorable.

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

¹²⁵ Generic drugs also require FDA approval, but generic equivalents of previously approved products can win approval through a streamlined “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).

more of their products. But this is not the only way to go.

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 to generate information for the public about the effects of drugs, such as the HRT study funded by NIH. Currently the National Institute of Alternative Medicine is conducting clinical trials on some popular herbal remedies and nutraceuticals, like chondroitin and glucosamine sulfate for arthritis, that have been permitted to get to 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 NIAM trials may indicate what we might 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 rather than on the public. Perhaps public resources should be deployed selectively to fortify the information base in areas where regulation is unlikely to lead private firms to conduct the necessary trials. This might justify the sometimes maligned distinction in current law between minimally regulated health products (such as vitamins and herbal remedies) and heavily regulated drugs. Although the distinction makes no 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 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. Instead, we place the burden on the government to show that these products are unsafe, and rely on government to pay for the testing.

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 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 inexperienced juries adds further noise 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 FDA has been to protect consumers from dangerous or fraudulently marketed products. But as the practices and statutory authorities of FDA have evolved, it 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 less distinct over time. Sometimes 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 lengthened, cutting further into product patent terms, and as industry “evergreening” strategies to secure additional follow-on patents have proven unsuccessful. Even 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 FDA’s current regulatory authorities make more sense from the perspective of promoting innovation than from the perspective of protecting patients. At the same time, examination of FDA regulation from the perspective of innovation 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.