7 HOUS. J. HEALTH L. & POL'Y 379–410 R

ISSN 1534-7907

PHARMACEUTICAL REFORMULATION: THE GROWTH OF LIFE CYCLE MANAGEMENT

Rebecca S. Yoshitani, J.D. and Ellen S. Cooper, J.D., LL.M.*

I. INTRODUCTION

The financial health of large, brand-name pharmaceutical companies, often referred to as "Big Pharma," relies heavily on portfolios of drugs grossing in excess of one billion dollars annually. Research and development of these "blockbuster drugs" require a tremendous investment of resources. According to the Pharmaceutical Research and Manufacturers of America ("PhRMA"), "only one of every 10,000 potential medicines investigated by America's research-based pharmaceutical companies makes it through the research and development pipeline and is approved for patient use by the United States Food and Drug Administration ("FDA")."[1] Obtaining FDA approval takes an average of ten to fifteen years of research and development and may cost over $800 million.[2]

Revenues realized by Big Pharma companies are directly related to the exclusive rights to market blockbuster drugs. For example, in August 2001, Eli Lilly sustained an unprecedented financial blow when its blockbuster antidepressant, Prozac, lost patent protection.[3] Although in 2000 Prozac sales had constituted a quarter of Lilly's $10.8 billion in revenues, by the end of the third quarter of

* Rebecca S. Yoshitani, a member of the Maryland Bar, is also admitted to practice before the United States Patent and Trademark Office. Ellen S. Cooper is an Assistant Attorney General and Chief of the Antitrust Division for the State of Maryland. The authors wish to thank Meredyth Smith Andrus for her many helpful edits and suggestions, and Karen Wadding for her much appreciated assistance. The views expressed are the authors' alone and are not necessarily the views of the Attorney General of Maryland.

[1] PhRMA, INNOVATION, http://www.phrma.org/innovation (last visited Sept. 23, 2007).

[2] *See id*.; Mark D. Shtilerman, *Pharmaceutical Inventions: A Proposal for Risk-Sensitive Rewards*, 46 IDEA 337, 348–50 (2006); Joseph A. DiMasi, Ronald W. Hansen & Henry G. Grabowski, *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151 (2003). *But see* PUBLIC CITIZEN CONGRESS WATCH, RX R & D MYTHS: THE CASE AGAINST THE DRUG INDUSTRY'S R & D "SCARE CARD," (July 2001), http://www.citizen.org/documents/acfdc.pdf (disputing PhRMA's cost estimates).

[3] *Lilly to Miss 4Q, '02 Marks*, CNN.com, Oct 3, 2001, http://edition.cnn.com/2001/BUSINESS/10/03/lilly/index.html.

2001, sales of Prozac had plunged sixty-six percent.[4] Erosion of that branded drug's market in favor of a generic was the most severe Big Pharma had yet experienced and foretold increasing losses of market share to generic substitution.[5]

In order to protect market share, pharmaceutical companies engage in "reformulation." Through reformulation, a drug company alters characteristics of a brand-name drug just enough to qualify for a new patent under patent examination procedures of the United States Patent and Trademark Office ("PTO"), while keeping enough characteristics the same to use previous clinical testing results for the purpose of FDA approval. The company lists the new patent in the FDA Orange Book[6] under either the existing or new brand, and then promotes the drug as "improved" in some fashion. Ultimately, the pharmaceutical firm is able to retain its market exclusivity for the drug, which would have been lost to generic substitution when the original patent expired.

The substantial information "gap" between PTO and FDA approvals creates ample opportunity for regulatory abuse. The PTO has no authority to require FDA review prior to patent approval, and FDA approval is effectively free from formal patent analysis.[7] Brand holders may be tempted to list improper patents and initiate bad-faith infringement litigation in order to extend market protection well beyond their lawful right. Additionally, even when reformulation is justifiable, patenting and listing the improvement as part of a larger scheme to prevent generic entry may also violate antitrust laws.

Part II of this paper discusses the law applicable to pharmaceutical reformulation while Part III explains the categories of reformu-

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[4] John Simons, *Lilly Goes Off Prozac*, FORTUNE MAGAZINE, June 28, 2004, *available at* http://money.cnn.com/magazines/fortune/fortune_archive/2004/06/28/374398/index.htm.

[5] *See* Lilly, *supra* note 3; Selena Class, *Pharma Reformulates,* 83 CHEM. & ENG. NEWS 15 (2005) (noting that six billion-dollar-plus drugs lost U.S. patent exclusivity during 2006: Pfizer's antidepressant Zoloft, Merck's cholesterol-reducing Zocor, Sanofi-Aventis' hypnotic Ambien, Bristol-Myers Squibb's cholesterol-reducing Pravachol, Novartis' antifungal Lamisil, and GlaxoSmithKline's anti-nausea drug Zofran).

[6] CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE (2007) (commonly known as the "Orange Book") [hereinafter *Orange Book*].

[7] 35 U.S.C. §§ 1 et seq. Applications for FDA Approval to Market a New Drug, 68 Fed. Reg. 36,676 (June 18, 2003) (codified at 21 C.F.R. § 314). The FDA has specifically declined to establish in its regulations "a mechanism for review of submitted patent information to determine, at least on a very general basis, applicability to the particular NDA in question." Abbreviated New Drug Application Regulations, Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,343 (Oct. 3, 1994).

lation, how pharmaceutical companies attempt to protect their interests in the reformulated product, and the antitrust issues that may arise. A case study for each category is provided.[8] Finally, Part IV suggests improvements to the current system.

II. APPLICABLE LAW

A. Patent law and PTO regulations

"*Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.*"[9]

The PTO awards patents to inventions that are novel, nonobvious, and useful.[10] Essentially, a "novel" invention is one that was not known or used by another in the United States or described in a patent or printed publication in any country before the applicant reduced the invention to practice.[11] Obviousness is a legal conclusion based on analysis regarding (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) the secondary considerations of nonobviousness.[12] Utility simply means that the invention may be put to some use, unless one of ordinary skill in the art would reasonably doubt this possibility.[13]

In exchange for disclosing the invention to the public, including how the invention is made and the best mode for making use of the invention, the applicant is awarded what is often termed a "legal monopoly" in the form of a patent, which is the right to exclude others from making, using, and/or selling the invention in the way described in the patent for a limited amount of time.[14] Currently,

[8] For additional case histories of reformulation abuse, see Andrew A. Caffrey, III & Jonathan M. Rotter, *Consumer Protection, Patents and Procedure: Generic Drug Market Entry and the Need to Reform the Hatch-Waxman Act*, 9 VA. J.L. & TECH. 1 (2004).

[9] 35 U.S.C. § 101 (1952).

[10] *Id*. at §§ 101–03.

[11] *Id*. at § 102 (1952). *See generally* 1 DONALD S. CHISUM, CHISUM ON PATENTS (2006) (addressing specifically in Chapter 3 the requirements for novelty).

[12] Graham v. John Deere Co., 383 U.S. 1, 17–18 (1966).

[13] 35 U.S.C. § 101; *In re* Brana, 51 F.3d 1560, 1564 (Fed. Cir. 1995).

[14] *See* 35 U.S.C. § 112 (1975) (describing requirements for enablement and best mode); Dawson Chem. Co. v. Rohm & Haas Co., 448 U.S. 176, 215 (1980); *see also* Mark A. Lemley & Carl Shapiro, *Probabilistic Patents*, 19 J. ECON. PERSPECTIVES 75 (2005).

that term begins the date the patent issues and ends twenty years from the date the patent application was filed.[15]

B. Drug laws and FDA regulations

Before the FDA can approve a new drug for sale and marketing in the U.S., the applicant or "sponsor" must conduct laboratory, animal, and human clinical studies to prove to the FDA's satisfaction that the new drug is safe and effective in its proposed use(s), and that the benefits of the drug outweigh the risks.[16] According to the FDA, this process takes an average of eight-and-a-half years.[17] The sponsor then files a New Drug Application ("NDA") including the studies, chemistry of the drug, safety information, manufacturing information, patents, samples, and labeling.[18] Once the application is sufficiently complete, a team of physicians, pharmacologists, toxicologists, chemists, statisticians, and microbiologists at the FDA's Center for Drug Evaluation and Research reviews the application.[19] Drugs that are new chemical or molecular entities, that have narrow therapeutic ranges, that represent the first approval for the applicant, or that are sponsored by a company with a history of manufacturing problems may also require manufacturing site inspections.[20] Because clinical testing and regulatory review by the FDA take considerably longer to complete than patent approval by

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[15] 35 U.S.C. § 154(a) (2002). Given the amount of time it generally takes to prosecute a patent, the effective term of a patent is likely to be 17–18 years. *See* HERBERT HOVENKAMP, MARK D. JANIS & MARK A. LEMLEY, 1 IP AND ANTITRUST § 2.2a3 (Supp. 2007) (noting that the period is from the date of patent approval to 20 years from the earliest U.S. filing date). Patent term extensions are available when the patent application process is delayed within the PTO, or when commercial marketing and/or use of the drug is delayed due to regulatory review by the FDA. 35 U.S.C. § 156 (2007).

[16] CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN., NEW DRUG APPLICATION (NDA) PROCESS, *available at* http://www.fda.gov/cder/regulatory/applications/nda.htm#FDA%20Guidances (last visited Sept. 12, 2007).

[17] CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN., FROM TEST TUBE TO PATIENT: PROTECTING AMERICA'S HEALTH THROUGH HUMAN DRUGS (2007), *available at* http: //www.fda.gov/fdac/special/testtubetopatient/studies.html (last visited Sept. 23, 2007).

[18] CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN., NEW DRUG APPLICATION, *available at* http://www.fda.gov/cder/handbook/ndabox.htm (last visited Sept. 12, 2007).

[19] CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN., NDA REVIEW PROCESS APPLICATION, *available at* http://www.fda.gov/cder/handbook/nda.htm (last visited Sept. 12, 2007) (see flow chart and attached links).

[20] CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN., COMPLIANCE PROGRAM GUIDANCE MANUAL, PROGRAM 7346.832, *available at* http://www.fda.gov/cder/gmp/PAI-7346832.pdf (last visited Sept. 12, 2007).

the PTO, the effective marketing period for an NDA under patent protection is typically between eleven and twelve years.[21]

Under the Hatch-Waxman Act,[22] the FDA approves an Abbreviated New Drug Application ("ANDA") for a generic version of a brand-name drug without requiring costly and duplicative clinical trials by recognizing bioequivalence to a drug with an existing NDA.[23] Essentially, bioequivalent drugs have no significant difference in the rate and extent to which the active ingredient becomes available in the body when administered at the same effective dose under similar conditions.[24] Hatch-Waxman decreased the time lag between expiration of the brand-name drug patent and FDA ap-

[21] CONGRESSIONAL BUDGET OFFICE, HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY: A CBO STUDY 38 (1998). Patent term extensions were enacted in 1985 to allow NDA applicants to recoup some of the marketing time lost during review. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended at 21 U.S.C. § 355 (1994)) (amending 35 U.S.C. § 156); OFF. OF TECHNOLOGY ASSESSMENT, PHARMACEUTICAL R&D 83 ("According to data that the Congressional Budget Office obtained from the Patent and Trademark Office, the average patent term remaining after FDA approval was 11.5 years for the fifty-one drugs approved between 1992 and 1995 that received a Hatch-Waxman extension. For drugs approved between 1978 and 1982, the average patent term remaining was just over nine years.").

[22] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended at 21 U.S.C. § 355 (1994)); *see* Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108–173, 117 Stat. 2066 (2003) (amending The Hatch-Waxman Act in 2003 to close some perceived loopholes).

[23] CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN., ABBREVIATED NEW DRUG APPLICATION (ANDA) PROCESS FOR GENERIC DRUGS, *available at* http://www.fda.gov/cder/regulatory/applications/ANDA.htm (last visited Sept. 23, 2007). For a more detailed description of the Hatch-Waxman Act, see Elizabeth Stotland Weiswasser & Scott D. Danzis, *The Hatch-Waxman Act: History, Structure, and Legacy*, 71 ANTITRUST L.J. 585 (2003). *See also* Elizabeth Powell-Bullock, *Gaming the Hatch Waxman System: How Pioneer Drug Makers Exploit the Law to Maintain Monopoly Power in the Prescription Drug Market*, 29 J. LEGIS. 21 (2002). For a description of the 2003 amendments, see Andrew H. Berks, *Antitrust Aspects of the "Access to Affordable Pharmaceuticals" Act: Incentives for Generics Out the Window?*, 16 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 1305 (2006); Stephanie Greene, *A Prescription for Change: How the Medicare Act Revises Hatch-Waxman to Speed Market Entry of Generic Drugs*, 30 J. CORP. L. 309 (2005).

[24] CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (27th ed. 2007), *available at* http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm (last visited Sept. 12, 2007). The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman) assumes that bioequivalent drug products are therapeutically equivalent and interchangeable. *Id*. By submitting results of one of the approved studies under 21 C.F.R. § 320.24, including: (1) pharmacokinetic (PK) studies; (2) pharmacodynamic (PD) studies; (3) comparative clinical trials; and (4) in-vitro studies, the sponsor can prove that the drug has the same "bioavailability" as the reference drug and thereby qualify as "bioequivalent." *Id*.

proval of the generic drug from between three and four years to a matter of months.[25]

The FDA publishes information about approved NDAs in the Orange Book.[26] The FDA permits NDA holders to list valid patents on the drug itself, the drug in combination with other components, and the method of treating a medical condition.[27] Additionally, the FDA lists generic drugs which, having "therapeutic equivalence," may be substituted by the dispensing pharmacist.[28] A "therapeutically equivalent" generic formulation is both bioequivalent and pharmaceutically equivalent to the brand-name formulation.[29] According to the FDA, "bioequivalent" formulations are likely to have equivalent clinical effect and no difference in their potential for adverse effects in patients; "pharmaceutically equivalent" drugs contain the same active ingredients, the same dosage and route of administration, and the same strength or concentration.[30]

In order to control drug costs, nearly every state encourages or mandates the substitution of generic drugs.[31] Generally, state laws and regulations reference generic drugs as listed in the Orange Book.[32] Managed health care plans offer financial incentives for generic substitution.[33]

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[25] CONGRESSIONAL BUDGET OFFICE, *supra* note 21, at 39. According to the CBO study, "the pre-Hatch-Waxman figure is based on the CBO's analysis of generic entry for eleven nonantibiotic drugs approved after 1962. The post-Hatch-Waxman figure is based in part on Henry Grabowski & John Vernon, *Longer Patents for Increased Generic Competition in the U.S.: The Hatch-Waxman Act After One Decade*, PHARMACOECONOMICS (1996)."

[26] *Orange Book*, *supra* note 6.

[27] 21 C.F.R. § 314.53 (1999). These types of patents are referred to as "ingredient" patents for the drug, "formulation and composition" patents for the drug in combination with other components, and "method of use" patents for the method of treating a medical condition. *Id*. The patent listings must be submitted within thirty days of the NDA submission (or if the patent is issued after NDA submission, within thirty days of the patent being issued) in order to be considered "timely filed" for ANDA certification purposes. ANDA holders are not required to make a certification to an untimely filed patent if the generic application is submitted before the patent. *Id*.

[28] CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, *supra* note 24. The FDA lists those drugs which it has analyzed and found therapeutically equivalent; individual states establish the laws and regulations which reference the Orange Book and permit actual substitution by the pharmacist. *Id*.

[29] *Orange Book*, *supra* note 6.

[30] Drugs@FDA Glossary of Terms, http://www.fda.gov/cder/drugsatfda/glossary.htm (last modified Jan. 4, 2007).

[31] *Orange Book*, *supra* note 6.

[32] *Id.*

[33] *See* Preferred Care, http://www.preferredcare.org/faq/faq_tiereddruglist.html (last visited Oct. 16, 2007) (stating that drugs are separated into "tiers" for the purpose of copay-

When a generic company submits an ANDA, it must certify one of four conditions regarding possible patent protection of the NDA: (1) the brand-name manufacturer has not filed patent information with the FDA ("Paragraph I certification"); (2) the registered applicable patent(s) have expired ("Paragraph II certification"); (3) the patent will expire on a particular future date ("Paragraph III certification"); or (4) the patent is invalid and/or will not be infringed by the generic manufacturer's product ("Paragraph IV certification").[34] If the generic company submits a Paragraph IV certification, it must promptly notify the patent holder of the certification.[35] By statute, this act of filing the certification acts as constructive infringement.[36] The patent holder then has forty-five days to initiate a patent infringement action against the generic applicant.[37] If the patent holder does bring suit, the FDA is automatically barred from granting approval of any ANDA until the first of the following events: (1) thirty months following the patent holder's receipt of the Paragraph IV certification; (2) the patent expires; or (3) the patent is held invalid or not infringed.[38]

The first generic company to file a Paragraph IV certification gains a huge strategic and financial advantage: entitlement to 180 days of marketing exclusivity over other Paragraph IV filers.[39] Consequently, if the brand-name company can stay approval of the first ANDA by a patent infringement action, it likewise delays approval of all other generic applicants.[40]

Abuses of government process in order to unlawfully extend product market exclusivity fall into three basic approaches: (1) the brand-name holder obtains and lists an invalid patent in the Orange

ment); *Carefirst Blue Cross Blue Shield Expands Drug Plans*, BALT. SUN, Oct. 24, 2006 at 2D (explaining that the insurance company will offer an option on group policies for zero copayments on generic prescriptions, but $25 and $45 on various brand names).

[34] 21 U.S.C. § 355(j)(2)(A)(vii) (2007).

[35] *Id*. at § 355(j)(2)(B).

[36] 35 U.S.C. § 271(e)(2) (2006) (allowing the patent holder to bring a cause of action based on the ANDA filing rather than on actual use, manufacture, or sale of the infringing product).

[37] *Id*. at § 271(e)(5).

[38] 21 U.S.C. § 355(j)(5)(B)(iii) (2007) (If the patent holder does not bring suit within the forty-five day window, it may still sue for patent infringement. It simply loses its right to obtain the thirty-month stay.).

[39] *Id*. at § 355(j)(5)(B)(iii)(IV).

[40] *Id.*

Book;[41] (2) the brand-name holder obtains and lists a valid patent, but the patent is not eligible to be listed in the Orange Book;[42] and (3) the brand-name holder lists a valid patent, which on its face covers the drug and meets FDA approval for listing, but then institutes an infringement suit against a generic which has clearly succeeded in "designing around" the patent.[43] Simply put, these three forms of abuse involve manipulating the PTO, the FDA, and the judicial process.

C. Antitrust Laws

"*Every contract, combination . . . or conspiracy, in restraint of trade or commerce among the several States . . . is hereby declared to be illegal . . . .*"[44] Nor shall any person "*monopolize, or attempt to monopolize, or combine or conspire with any other person or persons, to monopolize any part of the trade or commerce among the several States . . . .*"[45]

Antitrust laws provide the governing rules of competition in a free market.[46] However, enhancing consumer welfare is its central goal.[47] Competition leads to "the optimum mix of products and services in terms of price, quality, and consumer choice."[48] Both antitrust law and patent law serve the complementary aims of

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[41] *See, e.g.*, 35 U.S.C. § 102(b) (barring on-sale patenting); Walker Process Equip. v. Food Mach. & Chem., 382 U.S. 172 (1965) (holding there is fraud when the patent application has materially misrepresented information about the application to the PTO).

[42] *See, e.g.*, FTC, *Wrongful "Orange" Book Listing Raises Red Flag with FTC; Leads to Consent Order with Biovail Corp. Concerning its Drug Tiazac*, *available at* http://www2.ftc.gov/opa/2002/04/biovailtiazac.shtm (Apr. 23, 2002). This may occur when the patent covers a product or method of use not approved by the FDA, or is a type of patent, like a manufacturing process or product-by-process patent, that the FDA has specifically declared ineligible for listing. *Id*. In these cases, the brand-name holder fraudulently lists an ineligible patent and initiates an infringement suit in order to evoke a Hatch-Waxman thirty-month delay. *Id*.

[43] This abuse occurs when the brand holder lists a valid patent, and the generic applies for an ANDA based on a formulation which does not infringe the patent, either literally or under the doctrine of equivalents, yet the brand holder initiates an infringement suit in bad faith.

[44] 15 U.S.C. § 1 (2006).

[45] *Id*. at § 2.

[46] *See* N. Pac. Ry. v. United States, 356 U.S. 1, 4 (1958) ("The Sherman Act was designed to be a comprehensive charter of economic liberty aimed at preserving free and unfettered competition as the rule of trade.").

[47] *See* Robert H. Lande, *Consumer Choice as the Ultimate Goal of Antitrust*, 62 U. PITT. L. REV. 503, 503–04 (2001).

[48] FTC, TO PROMOTE INNOVATION: THE PROPER BALANCE OF COMPETITION AND PATENT LAW AND POLICY 3 (Oct. 2003), *available at* http://www.ftc.gov/os/2003/10/innovationrpt.pdf.

promoting innovation and enhancing consumer welfare.[49] Nevertheless, there is a tension between the two.[50]

Enforcement of a patent obtained through knowing and willful fraud may violate Section 2 of the Sherman Act, eliciting a *Walker Process* claim.[51] The elements of a *Walker Process* claim are that: (1) the patent holder knowingly and willfully omitted or misrepresented material facts to the PTO in procuring the patent; (2) the patent would not have issued "but for" the fraud; and (3) the patent holder has monopoly power or the dangerous probability of achieving monopoly power.[52] A related Section 2 theory focuses on a patent holder's initiation of litigation to enforce a patent it knows to be invalid.[53] The plaintiff must prove the defendant's bad faith in initiating litigation by clear and convincing evidence.[54] Thus, the fraud on the PTO itself does not give rise to an antitrust violation, nor does attempted enforcement of an invalid patent.[55] The thrust of the violation is monopolization or attempted monopolization of a relevant market, accomplished by those means.[56]

Although, under the *Noerr-Pennington* doctrine,[57] petitioning government through use of judicial processes is immune from antitrust liability, sham litigation is not immune. In *Professional Real Estate Investors, Inc. v. Columbia Pictures Industries, Inc.* ("*PRE*"), the Court held that litigation is sham conduct if the suit is objectively baseless (i.e., no reasonable litigant could realistically expect to succeed on the merits).[58] The Court, however, explicitly refused to de-

[49] *Id.* at 7 (quoting FTC Chairman Timothy J. Muris, Remarks at the American Bar Ass'n Antitrust Fall Forum: Competition and Intellectual Property Policy: The Way Ahead (Nov. 15, 2001)).

[50] *See* Lara J. Glasgow, *Stretching the Limits of Intellectual Property Rights: Has the Pharmaceutical Industry Gone Too Far?*, 41 IDEA 227, 230 (2001) (tension when intellectual property rights used to obtain unwarranted market power or to interfere with rightful competition). *But see* Bruce R. Genderson, *Settlements in Hatch-Waxman Act Patent Litigation: Resolving Conflicting Intellectual Property and Antitrust Concerns*, 3 SEDONA CONF. J. 43, 43–44 (Fall 2002) (policies often conflict).

[51] *See* Walker Process Equip. v. Food Mach. & Chem., 382 U.S. 172, 172 (1965).

[52] *See* HERBERT HOVENKAMP ET AL., *supra* note 15, at § 11.1.

[53] *See, e.g.,* Handguards, Inc. v. Ethicon, Inc., 601 F.2d 986 (9th Cir. 1975).

[54] *Id.* at 996.

[55] *See* HERBERT HOVENKAMP ET AL., *supra* note 15, at § 11.2e.

[56] *Id*.

[57] *See* E. R.R. Presidents Conference v. Noerr Motor Freight, Inc. 365 U.S. 127 (1961); United Mine Workers v. Pennington, 381 U.S. 657 (1965).

[58] 508 U.S. 49, 51 (1993).

cide whether *Noerr* permits the imposition of antitrust liability for fraud, as would be alleged in a *Walker Process* claim.[59]

Antitrust concerns arise when patent laws, FDA regulations, and the judicial process are abused in order to improperly extend the market exclusivity of pharmaceuticals. Brand-name companies have fraudulently filed suits alleging patent infringement in order to gain thirty months in the market, free from competition, despite clear statutory and judicially-created bars. Once the thirty months have passed, the brand-name companies may withdraw the infringement suit, thereby avoiding judicial review of the patent. An ANDA filer may file a counterclaim in an infringement action alleging patent abuse and antitrust violations. Frequently consumers, third party payors, and retailers file antitrust actions, consumer protection actions, or both, based upon the same conduct.[60]

III. REFORMULATION

Given the high cost of creating a completely new molecular compound,[61] it should come as no surprise that sixty percent of New Drug Applications submitted to the FDA during the 1990s were for drugs containing existing active ingredients.[62] Reformulation approaches can be classified into three categories: (1) reformulation of the molecular entity; (2) new deliveries; and (3) new indications.[63]

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[59] *Id.* at 61 n.6.

[60] *See, e.g.,* Walgreen Co. v. AstraZeneca Pharm. L.P., Civ. No. 1:06-cv-02084-RWR (D. D.C. filed Dec. 7, 2006) (plaintiffs were chain pharmacies); Penn. Employee Benefit Trust Fund v. Zeneca Inc., 2005 WL 2993937 (D. Del.) (third-party payors, consumer groups, and consumers brought actions under state consumer protection laws); Twin City Bakery Workers and Welfare Fund v. Astra Akiebolag, 207 F. Supp. 2d 221 (S.D.N.Y. 2002) (third-party payors brought antitrust actions); *see also In re* Buspirone Antitrust Litig., 210 F.R.D. 43, 46 (S.D.N.Y. 2002) (plaintiffs included generic drug manufacturers, direct purchasers, end-payors, consumer protection organizations, and States).

[61] New Molecular Entities (NMEs) are pharmaceuticals containing active ingredients that have not yet been approved for use in the United States. NAT'L INST. FOR HEALTH CARE MGMT., CHANGING PATTERNS OF PHARMACEUTICAL INNOVATION 5 (2002), http://www.nihcm.org/innovations.pdf (explanation of classes of drugs based on degree of innovation); *see supra* note 2.

[62] *See* CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN., NDAS APPROVED IN CALENDAR YEARS 1990–2004 BY THERAPEUTIC POTENTIALS AND CHEMICAL TYPES (2005), www.fda.gov/cder/rdmt/pstable.htm. *See generally* MARCIA ANGELL, THE TRUTH ABOUT THE DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT (2004).

[63] Pharmaceutical companies also reformulate brand-name drugs by combining them with other drugs, patenting the new combination and listing the combination patent in the Or-

A. Reformulation of the Molecular Entity

"Molecular entity reformulation" changes the molecular structure of a drug just enough that the new molecular form qualifies for a patent, yet it functions in the body sufficiently like the previous structure to constitute the "same" drug under the FDA guidelines for bioequivalency.[64] Applications for drugs that are bioequivalent to approved drugs may rely on previous clinical testing information in the approval process, thus saving enormous time and monetary investment.[65] Examples of molecular entity reformulation include the use of metabolites, chiral switching, and polymorphs.

1. Metabolites

In pharmaceutical terms, a metabolite refers to the chemical present after a chemical reaction takes place in the body.[66] Some drugs are administered to the patient in an inactive precursor or "prodrug" state and then break down in the body to form one or more metabolites. One of the resulting metabolites becomes the actual "active ingredient" that reacts again in the body to effect the ultimately desired treatment.[67] Administration of a drug in its primary metabolic state may have physiological advantages over administration of the prodrug.[68]

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ange Book. *See, e.g.*, McNeil-PPC, Inc. v. L. Perrigo Co., 337 F.3d 1362 (Fed. Cir. 2003). Discussion of new combination reformulation, however, is beyond the scope of this article.

[64] CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, *supra* note 24.

[65] *See, e.g.*, CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, WAIVER OF IN VIVO BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR IMMEDIATE-RELEASE SOLID ORAL DOSAGE FORMS BASED ON A BIOPHARMACEUTICS CLASSIFICATION SYSTEM (2000).

[66] *See* THE MERCK MANUAL OF DIAGNOSIS AND THERAPY 2526–27 (Mark H. Beers, M.D. et al. eds., Merck Publishing 18th ed. 2006).

[67] The product of that second reaction is a "secondary metabolite." Secondary metabolites discovered in nature (particularly in fungi and plants) have led to a wealth of new inventions including antibiotics (*e.g.*, penicillin, streptomycin), cancer treatment (Taxol), and an immunosuppressant used to prevent transplant rejection (immucyclosporin A). *See* K.C. Nicolaou, Dionisios Vourloumis, Nicolas Wissinger, & Pahil S. Baran, *The Art and Science of Total Synthesis at the Dawn of the Twenty-first Century*, 39 ANGEW. CHEM. INT. ED. 44 (2000).

[68] For example, the active ingredient in the antihistamine Allegra is a metabolite of the drug Seldane. When Seldane appeared to be related to potentially fatal heart conditions, the manufacturer, Hoechst Marion Roussel, increased warnings on Seldane and Seldane-D labels while the FDA instituted administrative procedures to remove the products from the market. Allegra appeared to provide nearly all of Seldane's beneficial effects without creating the cardiac side effects. Therefore, once Allegra and Allegra-D were approved, the FDA proposed that Hoechst remove all remaining Seldane products from the marketplace in favor of Allegra products. *See* FDA Talk Paper 97–67, *FDA Approves Allegra-D, Manufac-*

Litigation surrounding BuSpar illustrates patent abuse of a metabolite. Bristol-Myers Squibb ("BMS") obtained a patent which included a method for treating anxiety using the chemical buspirone, sold under the name BuSpar.[69] Near the end of the patent term, ANDAs were filed by several generic companies, including Mylan Pharmaceuticals Inc., Mylan Laboratories Inc., and Mylan Technologies Inc. (collectively "Mylan").[70] In obtaining a new patent, BMS claimed that using the metabolite to treat anxiety is different from treating anxiety with the prodrug version; however, for the purpose of listing the new patent with the existing NDA in the Orange Book, BMS claimed the two versions were therapeutically equivalent.[71] The FDA then suspended approval of ANDAs for generic buspirone.[72]

Mylan filed suit against both the FDA and BMS in the United States District Court for the District of Columbia, seeking injunctive relief requiring BMS to delist the metabolite patent and the FDA to approve its ANDA.[73] The FDA asked BMS to clarify whether the metabolite patent claimed *only* a method of administering a metabolite of buspirone.[74] If only the metabolite were claimed, the FDA could approve ANDAs on the prodrug. Contrary to what it claimed in the patent, however, BMS responded that "the [new] patent did not simply claim a method of using the metabolite, but also a method of using buspirone itself."[75] The FDA, relying on the statements of BMS and not the actual patent, informed BMS that the new patent was deemed Orange Book eligible.[76]

In *Mylan Pharmaceuticals, Inc. v. Thompson*, the Federal Circuit held that a generic manufacturer cannot obtain an order to delist a patent from the Orange Book.[77] The following year in *In re Buspirone*

turer to Withdraw Seldane from Marketplace (Dec. 29, 1997), *available at* http://www.fda.gov/bbs/topics/ANSWERS/ANS00843.html.

[69] *See In re* Buspirone Patent Litigation, 185 F. Supp. 2d 340, 342–43 (S.D.N.Y. 2002) (U.S. Patent No. 4,182,763 covered, "among other things, a method for treating anxiety by the use of a non-toxic anxiolytically-effective dose of buspirone" sold under the name 'BuSpar' as of 1986).

[70] *Id.* at 346.

[71] *Id.* at 342–50.

[72] *Id.* at 350.

[73] *See* Mylan Pharm., Inc. v. Thompson, 268 F.3d 1323 (Fed. Cir. 2001).

[74] Additionally, Mylan filed supplemental Paragraph IV certifications, claiming that the generic form of the prodrug BuSpar would not infringe the patent for the metabolite. *Id.*

[75] *Id.*

[76] *Id.*

[77] *Id.* at 1329–33.

Patent Litigation, the District Court for the Southern District of New York determined that during the prosecution of the patent, the examiner had refused to let the new patent include the prodrug version despite aggressive attempts by BMS to do so.[78] The court ruled that the metabolite patent did not include the prodrug version of BuSpar, and that BMS knew it.[79]

Subsequently, the Judicial Panel on Multidistrict Litigation consolidated four patent disputes and twenty-two antitrust actions, all of which involved the legality of BMS's conduct in obtaining and suing for infringement of patents for BuSpar in an attempt to monopolize the market for buspirone tablets.[80] In denying BMS's motion to dismiss, the court held that listing a patent in the Orange Book does not constitute petitioning activity for *Noerr-Pennington* purposes because the FDA performs only a "ministerial act" in reliance on the representations of the private party and does not perform any independent review of the matter.[81] Further, the court held that even if *Noerr-Pennington* were to apply, the plaintiffs had set out enough facts to support a *Walker Process* claim, which would cover fraudulently listing a patent in the Orange Book and subsequently filing lawsuits to exploit the listing for competitive advantage.[82] Finally, the court found that the position BMS took with respect to the scope of the second patent was "objectively baseless" within the meaning of *PRE*; hence, the litigation was a sham not entitled to *Noerr-Pennington* protection.[83] Early in 2003, BMS an-

[78] *See In re* Buspirone Patent Litigation, 185 F. Supp. 2d at 355–59 (specifically, the patent examiner found that the prodrug version was ineligible for patenting under the "on-sale bar rule," because the prodrug was offered for sale or sold in the United States more than one year prior to the filing date of the patent application).

[79] *Id.*

[80] The plaintiffs included generic drug manufacturers, direct purchasers, end-payors, consumer protection organizations and thirty states. *In re* Buspirone Patent Litigation and *In re* Buspirone Antitrust Litigation, 185 F. Supp. 2d 363, 365–66 (S.D.N.Y. 2002). All of the complaints alleged that BMS attempted to or did monopolize the market in buspirone tablets by, *inter alia*, listing a newly-obtained patent in the Orange Book less than one day before its existing patent expired; fraudulently misrepresenting to the FDA that the new patent covered uses of buspirone and that a reasonable claim of patent infringement could be asserted against generic producers of buspirone; and bringing patent infringement actions against generic competitors to trigger a thirty-month stay of the FDA's approval of the generics' ANDAs. *Id*. at 366.

[81] *Id.* at 369–73.

[82] *Id.* at 373.

[83] *Id.* at 375–76. The court did find that the federal antitrust claims arising from the Schein settlement were barred by the four-year statute of limitations. *Id.* at 379–80.

nounced that the antitrust litigation settled for a total of $535 million.[84]

2. *Chiral Switching*

While the specific bonding sequence of atoms within a molecule gives the molecule its common chemical name, some molecules can have different three-dimensional arrangements in space.[85] When two such arrangements are structurally mirror images of each other, they can be designated as S- and R- enantiomers (i.e., the two "chiral" versions).[86] A 50:50 mixture of the two structures is referred to as a "racemic mixture."[87]

"Chiral switching" replaces a racemic mixture version of a drug with the single-enantiomer version.[88] Individually, each enantiomer may have markedly different activity in the body.[89] Patent applicants can claim a "purer" and, theoretically, more effective single-enantiomer version of an already approved racemic drug or a

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[84] Melody Petersen, *Bristol-Myers Squibb to Pay $670 Million to Settle Numerous Lawsuits*, N.Y. TIMES, Jan. 8, 2003, at C9 (BMS paid $535 million to resolve the BuSpar litigation and another $135 million to settle claims relating to the cancer drug Taxol).

[85] MILTON ORCHIN, ROGER S. MACOMBER, ALLAN R. PINHAS, & R. MARSHALL WILSON, THE VOCABULARY AND CONCEPTS OF ORGANIC CHEMISTRY 224–25 (2d ed. 2005).

[86] AMERICAN MEDICAL ASSOCIATION, GEOMETRIC ISOMERISM AND CHIRALITY: THE USAN PERSPECTIVE, http://www.ama-assn.org/ama/pub/category/15698.html (last modified Aug. 8, 2006). Enantiomer pairs are identified by how they rotate plane-polarized light. Several different conventions are used to identify the individual enantiomers, including: S- (for sinister, left) and R- (for rectus, right), L- (for levo, left) and D- (for dextro, right), or "+" and "-." Generic names of the enantiomer-based drugs often reflect their rotation. For example, esomeprazole (Nexium) is the "left-handed" enantiomer of racemic omeprazole (Prilosec), while levalbuterol (Xopenex) is the "left-handed" enantiomer of the racemic albuterol (Ventolin). The US Adopted Names (USAN) Council assigns generic names to all drugs that have entered clinical trials and have some commercial potential. *Id*.

[87] ORCHIN, MACOMBER, PINHAS & WILSON, *supra* note 84, at 251.

[88] Stephen C. Stinson, *Chiral Drugs*, CHEM. & ENG. NEWS, Oct. 23, 2000, at 55–78.

[89] For example, Thalidomide was first marketed in Europe in the 1960s as a sleeping pill and to treat morning sickness during pregnancy. Children around the world were born with major malformations, including missing limbs, because their mothers had taken the drug during early pregnancy. Recent testing in primates indicates that the S-enantiomer half of the mixture is responsible for the disastrous side effects. *See* U.S. CTR. FOR THE EVALUATION OF RISKS TO HUMAN REPRODUCTION (CERHR), U.S. FOOD & DRUG ADMIN., THALIDOMIDE, http://cerhr.niehs.nih.gov/common/thalidomide.html#History (last modified Dec. 21, 2005); H. J. Schmahl, Lennart Dencker, Claudia Plum, Ibrahim Chahoud & Heinz Nau, *Stereoselective Distribution of the Teratogenic Thalidomide Analogue EM12 in the Early Embryo of Marmoset Monkey, Wistar Rat and NMRI Mouse*, 70 ARCHIVES OF TOXICOLOGY 749, 749 (1996).

distinct therapeutic use for an individual enantiomer.[90] The patent for the single-enantiomer version is then listed in the Orange Book.

Although patent law has a conflicted history regarding enantiomers, current case law tends to view an enantiomer as "novel" and "nonobvious" compared to a previously disclosed racemic version with different characteristics, provided that the new version has properties that were not predictable.[91] Additionally, the FDA, recognizing instances in which toxicity has been linked to only one member of a pair of enantiomers, encourages developing a single-enantiomer from a racemic mixture that has already been studied.[92]

AstraZeneca used chiral switching to convert the market for the treatment of gastric acidity from Prilosec, a racemic mixture, to Nexium, a single-enantiomer version.[93] Following clinical testing, AstraZeneca scientists reported that Nexium was clinically superior to Prilosec in treating gastroesophageal reflux disease, or GERD, the most common acid-related disease.[94] However, the FDA's medical review of the submissions specifically found that AstraZeneca failed to demonstrate the superiority of Nexium over Prilosec.[95] Although the clinical tests established that Nexium is indeed active in healing

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[90] A. Maureen Rouhi, *Chirality at Work: Drug Developers Can Learn Much from Recent Successful and Failed Chiral Switches,* CHEM. & ENG. NEWS, May 5, 2003, at 56–61.

[91] A finding of obviousness regarding the enantiomer-based drug can be rebutted, provided the applicant proves the enantiomer has properties not obvious to one skilled in the art. Except where the art had advanced to the point that it is possible to predict with some "minimum reliability" the behavior of a given enantiomer, the enantiomer may be considered both novel and nonobvious. Eli Lilly & Co., Inc. v. Generix Drug Sales, Inc., 460 F.2d 1096, 1103 (5th Cir. 1972); *see* Application of May, 574 F.2d 1082, 1094 (Cust. & Pat. App. 1978).

[92] The FDA permits the applicant to apply for an abbreviated evaluation that compares existing knowledge of the racemic mixture to the pure enantiomer. No further studies are required if the toxicological profile of the single enantiomer product and the racemate are the same. CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN., FDA'S POLICY STATEMENT FOR THE DEVELOPMENT OF NEW STEREOISOMERIC DRUGS, GUIDANCE FOR INDUSTRY (1992), *available at* http://www.fda.gov/cder/guidance/stereo.htm (last modified July 06, 2005).

[93] Prilosec (omeprazole) Package Insert, AstraZencea, 2006, *available at* http://www.astrazeneca-us.com/pi/Prilosec.pdf (last modified Apr. 2007); Nexium (esomeprazole magnesium) Package Insert, AstraZeneca, 2006, *available at* http://www.astrazeneca-us.com/pi/Nexium.pdf (last modified Apr. 2007).

[94] Tore Lind, et al., *Esomeprazole Provides Improved Acid Control vs. Omeprazole in Patients with Symptoms of Gastro-oesophageal Reflux Disease,* 14 ALIMEN. PHARMACOL. & THER. 861 *passim* (2000) ("[Nexium] provides more effective acid control than [Prilosec], with reduced interpatient variability, thereby offering the potential for improved efficacy in acid-related diseases.").

[95] Medical Review, NDA application 21-153, Nexium (Esomeprazole Magnesium) Delayed-Release Capsules, at 4–5, *available at* http://www.fda.gov/cder/foi/nda/2001/21154_Nexium_medr_P1.pdf (Feb. 20, 2001); Letter, FDA/CDER to Kathryn D. Kross, As-

erosive esophogitis, the different dosage levels used (40 mg Nexium vs. 20 mg Prilosec) prevented the FDA from concluding that Nexium is clinically superior to Prilosec.[96] In fact, when the same 20 mg dose of each drug was administered, Nexium did not exhibit any clinical superiority over Prilosec.[97]

When several generic companies filed ANDAs containing Paragraph III certifications as to the basic patent for omeprazole and Paragraph IV certifications for 20 mg and 40 mg capsules of Nexium, AstraZeneca filed suit for infringement of six patents, thereby triggering a thirty-month delay in approval of any ANDA.[98] Although the patents were eventually found valid but not infringed,[99] the litigation delayed generic entry into the market for more than a year after the Prilosec patent expired.

On December 7, 2006, a number of pharmacy chains sued AstraZeneca alleging that it violated federal antitrust laws by introducing Nexium solely to protect its monopoly profits from generic competition.[100] According to the complaint, AstraZeneca engaged in a massive and deceptive promotional campaign to convert patients from Prilosec to Nexium before Prilosec lost its patent protection, despite knowing that Nexium is no more effective than Prilosec.[101] AstraZeneca then withdrew Prilosec from the prescription market by obtaining FDA approval to sell Prilosec over the counter (Prilosec OTC).[102] Finally, the complaint alleges that AstraZeneca artificially constricted the supply of Prilosec OTC in order to force patients to seek prescriptions for Nexium.[103]

3. Polymorphs

The FDA defines polymorphs as including "chemicals with different crystalline structures, different waters of hydration, solvents,

traZeneca, L.P., *available at* http://www.fda.gov/OHRMS/DOCKETS/dailys/03/oct03/101403/02p-0377-c000003-vol2.pdf (Feb. 20, 2001).

[96] Medical Review, NDA application 21-153, *supra* note 94.

[97] *Id.*

[98] *See In re* Omeprazole Patent Litigation, MDL No. 1291 at 1314 (S.D.N.Y. 2002).

[99] *In re* Omeprazole Patent Litigation, 84 Fed. App. 76, 76 (Fed. Cir. 2003).

[100] *See* Walgreen Co. v. AstraZeneca Pharm. L.P., Civ. No. 1:06-CV-02084-RWR (D.D.C., filed Dec. 7, 2006).

[101] *Id.* at 21–26.

[102] *Id.* at 29–31.

[103] *Id.* at 31.

and amorphous forms."[104] The active ingredient in a polymorph variation can be considered the bioequivalent of a referenced drug, notwithstanding differences in the physical forms of their active ingredient, if the drug performs the same way in the body as the referenced drug.[105]

In 1977, scientists at the British company Ferrosan obtained a U.S. patent for paroxetine and its salts which disclosed the drug's antidepressant properties.[106] Subsequently, Ferrosan developed a crystalline anhydrate salt of paroxetine and licensed it to SmithKline Beecham Corp. ("SK").[107] In 1985, a chemist at SK developed a hemihydrate crystalline form.[108] Claiming that the hemihydrate version was more stable than the anhydrate version, SK applied to the British Patent Office ("BPO") for a patent.[109] The BPO application identified both hemihydrate and anhydrate forms as well as mixtures using either form.[110] SK then filed for a patent in the United States claiming priority to the BPO application, but only claiming the hemihydrate.[111] In 1993, SK obtained FDA approval for paroxetine hydrochloride under the brand Paxil, listing the hemihydrate patent but not the original, broad paroxetine patent or any claim for the anhydrate.[112]

TorPharm, Inc., an affiliate of Apotex, later filed an ANDA for the anhydrate, including Paragraph IV certification stating the anhydrate would not infringe the U.S. patent for the hemihydrate.[113]

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[104] Applications for FDA Approval to Market a New Drug, 68 Fed. Reg. 36676, 36678 (June 18, 2003) (to be codified at 21 C.F.R. pt. 314). A "crystalline" substance is one whose atoms form a regular pattern over large distances. This regularity is usually measured by the diffraction of x-rays. Types of crystalline polymorphic structures include "hemihydrate," having two molecules of the base chemical to every molecule of H_2O; "trihydrate," having three molecules of water to every molecule of base chemical; and "anhydrate," having no water molecules attached. "Amorphous" refers to a mixture of structures whose atoms are not found in regular arrays, and, therefore, do not give crystalline patterns, even though the atomic ratios are the same.

[105] *Id*.

[106] U.S. Patent No. 4,007,196 (filed Feb. 8, 1977); *see* SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1334 (Fed. Cir. 2005).

[107] SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d at 1334.

[108] *Id.*

[109] *Id.*

[110] *Id.*

[111] *Id*. The application was issued as U.S. Patent No. 4,721,723 in 1988. *Id*.

[112] *Id.*; *see Orange Book*, *supra* note 6, at NDA 02-0031.

[113] Letter from Gary Buehler, Dir., Office of Generic Drugs, Ctr. For Drug Evaluation & Research, to Mary McDonald, U.S. Agent for TorPharm, Apotex Corp., *available at* http://www.fda.gov/cder/foi/appletter/2003/75356ap.pdf (Jul. 30, 2003).

SK initiated an infringement action, asserting that this ANDA would infringe the U.S. hemihydrate patent because the process of manufacturing anhydrate tablets would inherently produce at least trace amounts of the hemihydrate.[114]

SK's argument backfired. If the hemihydrate version was inherent in the anhydrate form, as described in the British patent, then it was already enabled and in use before SK applied for the U.S. hemihydrate patent.[115] The original U.S. patent, which disclosed how to make the anhydrate version, must have inherently produced the hemihydrate even though the hemihydrate was not "discovered" until years later.[116] The hemihydrate patent was, therefore, invalid as inherently anticipated.[117]

Meanwhile, SK continued to apply for additional patents related to the anhydrous polymorph of paroxetine, listing the patents in the Orange Book as each patent issued.[118] Generic competitors attempting to obtain ANDAs for paroxetine were required to file Paragraph IV certifications each time SK listed a new patent.[119] SK responded to each certification with infringement actions, eventually compiling a total of seven different actions.[120]

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[114] SmithKline Beecham Corp. v. Apotex Corp., 247 F. Supp. 2d 1011, 1024 (N.D. Ill. 2003).

[115] *See* Bristol-Myers Squibb Co. v. Ben Venue Labs Inc., 246 F.3d 1368, 1376 (Fed. Cir. 2001).

[116] SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1346 (Fed. Cir. 2005). The case history generated several approaches, from a special equitable defense articulated by Judge Richard Posner in the district court opinion, to inherent anticipation as articulated by Judge Rader on rehearing. *Id*. at 1343–46. Judge Gajarsa concurred in that opinion, focusing on invalidity under 35 U.S.C. §101, because the claims necessarily encompassed unpatentable subject matter, based upon the same scientific principles that supported SK's theory of infringement of that claim. *Id*. at 1347–52. Judge Newman had earlier dissented, asserting that the majority panel opinion improperly enlarged the doctrine of inherent anticipation. *See* SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1328 (Fed. Cir. 2005) (dissenting from order declining rehearing en banc). The case also introduced a new potential legal concept: "patentee induced infringement." *See* Christopher Cotropia, *Observations on Recent Patent Decisions: the Year in Review 2005*, 88 J. PAT. & TRADEMARK OFF. SOC'Y 46, 58–59 (Jan. 2006).

[117] There is no requirement that "a person of ordinary skill in the art at the time of invention would have recognized the inherent disclosure" at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *See* Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency).

[118] Stop & Shop Supermarket Co. v. SmithKline Beecham Corp., 2005 WL 1213926 at *2 (E.D. Pa. May 19, 2005).

[119] *Id*.

[120] SK filed additional patent infringement actions against Apotex in 1999, 2000, and 2001. *See* SmithKline Beecham Corp. v. Apotex Corp., et al., Civ.A.No. 99-CV-4304 (E.D. Pa.);

In several class action antitrust suits on behalf of direct and indirect purchasers of Paxil nationwide, plaintiffs asserted monopolization claims under Section 2 of the Sherman Act alleging that SK: (1) prosecuted baseless and sham lawsuits; (2) made intentional misrepresentations to the PTO; and (3) made false and misleading representations to the FDA.[121] The effect of these actions was to exclude or delay generic entry into the market for Paxil. In court-approved settlement agreements, SK paid over $165 million.[122] SK paid an additional fourteen million dollars to settle the claims of government purchasers.[123]

B. New Deliveries

Brand name pharmaceutical companies may create a "new" drug product that is the bioequivalent to an original drug (i.e., acting the same way in the body), but in a new delivery method not

SmithKline Beecham Corp. v. Apotex Corp., et al., Civ.A.No. 00-CV-4888 (E.D. Pa.); SmithKline Beecham Corp. v. Apotex Corp., et al., Civ.A.No. 01-CV-0159 (E.D. Pa.). SK also filed two patent infringement actions against Geneva Pharmaceuticals, Inc. in 1999 and 2000. *See* SmithKline Beecham Corp. v. Geneva Pharm., Inc., et al., Civ.A.No. 99-CV-2926 (E.D. Pa.) and SmithKline Beecham Corp. v. Geneva Pharm., Inc., et al., Civ.A.No. 00-CV-5953 (E.D. Pa.). SK filed a patent infringement action against Zenith Goldline Pharmaceuticals, Inc. in 2002. *See* SmithKline Beecham Corp. v. Zenith Goldline Pharm., Inc., et al., Civ.A.No. 00-CV-1393 (E.D. Pa.). SK also filed a patent infringement action against Pentech Pharmaceuticals, Inc., in 2000. *See* SmithKline Beecham Corp. v. Pentech Pharm., Inc., et al., Civ.A.No. 1:00-02855 (N.D. Ill.). Finally, SK sued Alphapharm PTY, Ltd. in 2002. *See* SmithKline Beecham Corp. v. Alphapharm PTY, Ltd., et al., Civ.A.No. 01-CV-1027 (E.D. Pa.).

As noted by the Federal Circuit in SmithKline Beecham Corp. v. Apotex Corp., 439 F.3d 1312 (Fed. Cir. 2006), one of the additional patents, U.S. Patent No. 6,113,944, was a "product-by-process" patent. *In re* Thorpe, 777 F.2d 695, 698 (Fed. Cir. 1985). Product-by-process claims allow inventors to "claim an otherwise patentable product that resists definition other than by the process by which it is made." *Id*. at 697. However, patentability is always based on the product itself, not the process by which it is made. *Id*. Anticipation by an earlier product patent cannot be avoided by claiming the same product more narrowly in a product-by-process claim, which is exactly what SK had done in SmithKline Beecham Corp. v. Apotex Corp., 439 F.3d 1312, 1317 (Fed. Cir. 2006), citing U.S. Patent and Trademark Office, Manual of Patent Examining Procedure, § 2113 (8th ed., rev. Apr. 2005) [hereinafter MPEP] and *In re* Thorpe, at 698.

[121] Stop & Shop Supermarket Co. v. SmithKline Beecham Corp., No. Civ.A. 03-4578, 2005 WL 1213926, at *1 (E.D. Pa. May 19, 2005).

[122] *See id.* (direct purchasers settled for $100 million); Nichols v. SmithKline Beecham Corp., 2005-1 Trade Cas. (CCH) ¶ 74,762 (E.D. Pa. 2005) (indirect purchasers settled for $65 million).

[123] Maryland v. SmithKline Beecham Corp., Civ. No. 06-1298 (E.D. Pa., filed Mar. 27, 2006) (settlement on file at the Office of the Attorney General of Maryland).

considered "pharmaceutically equivalent" to the original.[124] The FDA processes old drugs using new deliveries as NDAs.[125] If an NDA sponsor of a new delivery drug declares bioequivalence to a previously approved drug,[126] the NDA sponsor, like an ANDA filer, may incorporate efficacy and safety data previously submitted to the FDA for the bioequivalent drug.[127] Consequently, reformulation by new delivery, particularly when incorporating a patentable delivery system, is an extremely attractive method of life cycle enhancement.[128]

In some cases, a pharmaceutical company completes the market switch to a new delivery system by discontinuing marketing of the previous form.[129] A discontinued drug is no longer available as a Reference Listed Drug (RLD) for ANDA filers.[130] Nothing currently forbids an NDA holder from unilaterally discontinuing a drug listing in the Orange Book.[131] Methods employed for reformulation by

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[124] Pharmaceutically equivalent drugs use the same dosage and route of administration, and in the same strength or concentration. CTR. FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., DRUGS @ FDA GLOSSARY OF TERMS (2007), http://www.fda.gov/cder/drugsatfda/glossary.htm (last modified Jan. 4, 2007). Pharmaceutically equivalent drugs may differ, however, in shape, release mechanism, scoring, and additives like coloring, flavoring, and preservatives. *Id*.

[125] New delivery techniques range from the complexities of ultra-refining and micro-encapsulating an intravenous drug so that the drug can be administered orally to simply changing the dosage strength. Protections for new deliveries include patents based on the new components added to the drug, and patents based on the way a medical condition is treated using the new delivery system. Patents based on the new components added to the drug are considered "compositions of matter" patents by the FDA, while patents based on the way a medical condition is treated using the new delivery system are considered "method" patents.

[126] *See* CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUS. BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR ORALLY ADMINISTERED DRUG PRODS. — GENERAL CONSIDERATIONS, REVISION 1 (2003).

[127] 21 U.S.C.A. § 355(j)(2)(A) (2003).

[128] As with other reformulation approaches, there is a growing secondary industry for companies specializing in developing new delivery systems for large pharmaceutical companies. For example, ALZA Corporation specializes in drug delivery solutions including oral, transdermal, implantable, and liposomal technologies. Orally administered drugs acquiring new patent protection based on ALZA technology include Concerta (Ritalin brand in extended release form, for ADHD treatment), Ditropan XL (for overactive bladders), Efidac 24 (extended release reformulation of Chlor-Trimeton Allergy), and Sudafed 24 Hour (decongestant). ALZA: Commercial Products *at* http://www.alza.com/alza/products (last visited Sept. 23, 2007).

[129] *See, e.g.,* Abbott Labs. v. Teva Pharm. USA, Inc., 432 F. Supp. 2d 408 (D. Del. 2006).

[130] *Id*. at 416, 418.

[131] In October 2000, FDA staff proposed procedures for making discontinued drugs generally available for referencing by ANDA filers, unless the drug or labeling was discontinued for safety or effectiveness. CTR. FOR DRUG EVALUATION & RESEARCH, DEP'T OF HEALTH AND

new delivery include changing the dosage form of the drug and changing the route of administration of the drug into the body.

1. Dosage Form

"Dosage form" refers to the physical form of a drug.[132] In determining dosage form, the FDA examines such factors as: (1) the physical appearance of the drug product; (2) the physical form of the drug product prior to dispensing to the patient; (3) the way the product is administered; (4) the frequency of dosing; and (5) how pharmacists and other health professionals might recognize and handle the product.[133] Over 75 dosage forms are listed in the Orange Book.[134]

Warner Chilcott acquired the rights to the branded drug Ovcon 35, a monophasic low-dose oral contraceptive containing estrogen and progestin, from Bristol-Myers Squibb in 2000, after the patent protecting the NDA for the Ovcon 35 tablet expired.[135] In 2003, Warner Chilcott received FDA approval for a patent-protected chewable tablet, which contained the identical active ingredients in a neutral, chewable carrier.[136] The move to a "new" dosage form, which could also be swallowed like the original tablet, enabled

HUMAN SERVS., GUIDANCE FOR INDUS. - REFERENCING DISCONTINUED LABELING FOR LISTED DRUGS IN ABBREVIATED NEW DRUG APPLICATIONS - DRAFT GUIDANCE (2000). The FDA never implemented this proposed Guidance for Industry, however.

[132] CTR. FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., Drugs@FDA Glossary of Terms, *available at* http://www.fda.gov/cder/drugsatfda/glossary.htm (last visited Sept. 12, 2007).

[133] CTR. FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., CDER Data Standards Manual, *available at* http://www.fda.gov/cder/dsm/index.htm (last modified Mar. 9, 2007).

[134] *Id*. Just as a "lozenge" is a different dosage form from a "lotion," "capsules" are different from "tablets." Even capsules have five different forms, including coated pellets, coated extended release, delayed release, and delayed release pellets. CTR. FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., CDER Data Standards Manual, Dosage Form, *available at* http://www.fda.gov/cder/dsm/DRG/drg00201.htm (last modified Dec. 15, 2006).

[135] *See* Fed. Trade Comm'n v. Warner Chilcott Holdings Co. III, Ltd., (D.D.C., complaint filed Nov. 7, 2005); Warner Chilcott website, http://www.warnerchilcott.com/products/ovcon.php (last visited Sept. 23, 2007).

[136] CTR. FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., LABEL AND APPROVAL HISTORY: OVCON CHEWABLE, FDA APPLICATION NO. (NDA) 02-1490 (2003), (protected by U.S. Patent No. 6,667,050 (filed June 12, 2001), *available at* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm (last visited Sept. 12, 2007)). The approved packaging directions informed women that the pill could be swallowed whole as in the previous formulation, or chewed and swallowed, which would then require the patient to drink a full 8 ounces of liquid immediately afterwards to insure that the full dose of medication reaches the stomach and no residue is left in the mouth. *Id*.

Warner Chilcott to discontinue the original NDA and switch the market to a new form based on an improved "ease of use" without losing any consumers who preferred the former dosage form. Moreover, once the NDA labeling information for the old "nonchewable" version was removed from the Orange Book, no generic brand could use it for reference. Meanwhile, Barr Laboratories was in the process of acquiring an ANDA for Ovcon 35.[137] In a noteworthy twist, Warner Chilcott contracted with Barr to refrain from entering the market with generic Ovcon 35 and to provide product exclusively to Warner Chilcott until Warner Chilcott could bring the chewable version online and discontinue the nonchewable NDA.[138]

In September 2006, the FTC filed for a preliminary injunction to require Warner Chilcott to continue marketing Ovcon tablets.[139] Warner Chilcott immediately waived the provision in its agreement with Barr that prevented Barr from introducing generic Ovcon, and Barr announced its plan to enter the market.[140] One month later, the FTC announced that it had agreed to settle its complaint against Warner Chilcott by means of permanent injunction.[141] State attorneys general also settled with Warner Chilcott, but their case and the FTC's case against Barr are still pending.[142]

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[137] *See* CTR. FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., Approval History ANDA 076238, *available at* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm (last visited Sept. 12, 2007). Barr received approval of its ANDA on April 22, 2004.

[138] In September 2001, Barr filed an ANDA with the FDA for a generic version of the Ovcon 35 tablets, intending to price the generic thirty percent lower than the branded Ovcon. FTC v. Warner Chilcott Holdings, Complaint, No. 1:05-CV-02179-CKK (D. D.C. 2005); FTC File No. 041 0034, *available at* http://www.ftc.gov/os/caselist/0410034/051107comp0410034%20.pdf (last visited Sept. 12, 2007). Allegedly, to forestall this threat and to protect Ovcon sales, Warner Chilcott, through its subsidiary Galen Chemicals Ltd., entered into a March 2004 agreement with Barr. Warner Chilcott held an option to pay Barr $20 million in return for which Barr would not enter the market for five years. *Id*. Barr, however, would be available as a supplier of Ovcon to Warner Chilcott upon request. *Id*. On November 7, 2005, twenty-one states, the District of Columbia and the Federal Trade Commission sued Warner Chilcott Corporation and Barr Pharmaceuticals under Section 1 of the Sherman Act for entering into an agreement that blocked generic competition for Ovcon. *Id*. In April 2006, Barr's generic version was approved and, shortly thereafter, Warner Chilcott paid Barr the $20 million. *Id*.

[139] Press Release, Fed. Trade Comm'n, Consumers Win as FTC Action Results in Generic Ovcon Launch, *available at* http://www.ftc.gov/opa/2006/10/chicott.shtm (Oct. 23, 2006).

[140] *Id.*

[141] *Id.*

[142] Press Release, Attorney General Gansler Announces Settlement with Maker of Popular Oral Contraceptive, *available at* http://www.oag.state.md.us/Press/2007/061307.htm (June 13, 2007); *see* FTC v. Warner Chilcott Holdings Co., Civ. Action No. 1:05-CV-02195-

2. *Route of Administration*

The FDA's Center for Drug Evaluation and Research maintains a list of standards for all routes of administration for drugs.[143] The Center has identified over 100 different routes of administration.[144] By changing the way a drug enters the body, a drug company creates a product that is considered pharmaceutically different from the original form.[145] Although this requires a new NDA, if the drug is the bioequivalent to a previously approved drug, the applicant can avoid most of the time and expense associated with clinical testing.[146]

For example, desmopressin acetate ("DDAVP") was first approved by the FDA for the treatment of diabetes insipidus and later as a treatment for bedwetting.[147] The original patent, licensed by Ferring B.V.,[148] taught that the drug could be administered to the patient through "peroral" and other applications.[149] In December 1985, Ferring's scientists filed the application for a new patent, which described administration of the drug through absorption in the gastrointestinal tract, and further described this method as an improvement over the previous methods of administration.[150] The PTO examiners of this application, believing that the earlier claimed "peroral" administration might inherently suggest administration through the gastrointestinal tract as well, suggested that the applicants provide evidence from a non-inventor to support the applicants' interpretation of "peroral" as absorption through the walls of

CKK (D. D.C. 2005); Colorado v. Warner Chilcott Holding Co., Civ. Action No. 1:05-CV-02210-CKK (D. D.C. 2005) (complaints filed Nov. 7, 2005).

[143] *See* CDER DATA STANDARDS MANUAL, *available at* http://www.fda.gov/cder/dsm/DRG/drg00301.htm (last modified Jan. 2007).

[144] CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN., *available at* http://www.fda.gov/cder/dsm/index.htm (last modified Mar. 9, 2007).

[145] CTR. FOR DRUG EVALUATION AND RESEARCH, FOOD & DRUG ADMIN., Approved Drug Products with Therapeutic Equivalence Evaluations, *supra* note 24.

[146] *See id*.

[147] Ferring Pharm., Other Products, http://www.ferringusa.com/other_products/ (last visited Sept. 23, 2007).

[148] U.S. Patent No. 3,497,491 (filed Sept. 14, 1967).

[149] "Peroral" is defined as "occurring through or by way of the mouth." MERRIAM-WEBSTER'S COLLEGIATE DICTIONARY (Merriam-Webster 11th ed. 2002). The FDA does not use the term "peroral" to describe a route of administration. Ferring B.V. v. Barr Labs, Inc., 437 F.3d 1181, 1183 (Fed. Cir. 2006).

[150] This application was eventually approved as U.S. Patent No. 5,047,398 (filed Dec. 17, 1985). Ferring B.V. v. Barr Labs, Inc., 437 F.3d at 1183.

a patient's mouth.[151] The applicants submitted five purportedly independent declarations, but only one declarant had no actual relationship with Ferring.[152] The patent issued in 1991.[153]

Ferring exclusively licensed the right to market and sell DDAVP to Sanofi-Aventis,[154] which obtained FDA approval for the NDA and listed the new patent in the Orange Book.[155] After Barr Laboratories filed an ANDA, including a Paragraph IV certification claiming that the new patent was invalid, Ferring filed an infringement action.[156] The district court granted Barr's motion for summary judgment on the grounds of inequitable conduct before the PTO.[157] Inequitable conduct, defined as a breach of duty to the PTO of "candor, good faith, and honesty,"[158] includes not only affirmative representations of material facts but also failure to disclose material information.[159] The Federal Circuit affirmed the summary judgment, noting that the declarations themselves were "highly material" in the decision to allow the patent to issue, the past relationships of the declarants and the applicants were significant, and multiple omissions were made with the deliberate intent to deceive.[160]

Nationwide direct and indirect purchaser class actions alleged that Ferring and its licensee Sanofi-Aventis unlawfully maintained a monopoly in the market for DDAVP by: (1) procuring a patent through fraud and/or inequitable conduct before the PTO; (2) improperly listing that patent in the Orange Book; (3) instituting and prosecuting sham litigation against two generic ANDA filers; and (4) filing a sham citizen's petition in order to delay FDA approval of

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[151] *See id.* at 1183–84.

[152] Four declarants had either been employed by or received research funding from Ferring, and the inventor participated in drafting two of the other declarations. None of this information was revealed to the patent examiners. *Id.* at 1185.

[153] U.S. Patent No. 5,047,398 (filed Dec. 17, 1985). The patent is due to expire on September 10, 2008.

[154] Ferring B.V. v. Barr Labs, Inc., 437 F.3d at 1183–84.

[155] *See Orange Book, supra* note 6, at NDA 01-9955.

[156] Ferring B.V. v. Barr Labs, Inc., No.7:02-CV-9851 CLB MDF 2005 WL 437981, at *1 (S.D.N.Y. Feb. 7, 2005).

[157] *Id.*

[158] Ferring B.V. v. Barr Labs, Inc., 437 F.3d at 1186 (citing Warner-Lambert Co. v. Teva Pharm. USA, Inc., 418 F.3d 1326, 1342 (Fed. Cir. 2005) (quoting Molins PLC v. Textron, Inc., 48 F.3d 1172, 1178 (Fed. Cir. 1995))).

[159] *Id*. at 1186; Ferring B.V. v. Barr Labs, Inc., 437 F.3d at 1186; Pharmacia Corp. v. Par Pharm. Inc., 417 F.3d 1369, 1373 (Fed. Cir. 2005).

[160] Ferring B.V. v. Barr Labs, Inc., 437 F.3d at 1188–95.

generic DDAVP tablets.[161] Plaintiffs claimed that, as a result of this conduct, they paid up to hundreds of millions of dollars more for DDAVP than if generic versions of the drug had been on the market.[162] However, on November 2, 2006, the district court dismissed the antitrust cases on several alternative grounds.[163] First, it ruled that the plaintiffs could not plead fraud with sufficient particularity to meet the requirements of Rule 9(b) of the Federal Rules of Civil Procedure based on the patent court's finding of inequitable conduct.[164] Alternatively, plaintiffs lacked standing to pursue a *Walker Process* claim in the absence of any attempt by the defendants to enforce the patent against them.[165] Finally, Sanofi-Aventis and Ferring filed infringement suits, not in bad faith, but in "a standard response to Hatch-Waxman," and had a First Amendment right to file a citizen's petition despite the foreseeable effect on generic entry.[166] An appeal is pending.[167]

C. New Indications

A drug company may acquire a patent for a "new indication," that is, a new method of use for an existing drug, in order to create a new and exclusive market.[168] Merely listing the new patent in the Orange Book under the existing NDA, however, will not block an ANDA from being approved for a generic corresponding to the old indications.[169] In *Bristol-Myers Squibb Co. v. Shalala*,[170] the Court of

[161] *In re* DDAVP Direct Purchaser Antitrust Litigation and *In re* DDAVP Indirect Purchaser Antitrust Litigation, No. 05-CV-2237 (CLB) (S.D.N.Y.) (order filed Nov. 2, 2006). Indirect purchasers also stated claims brought under state antitrust and consumer protection statutes.

[162] *Id.* at 3.

[163] *Id.*

[164] *See* Ferring B.V. v. Barr Labs., Inc., 437 F.3d at 1192.

[165] *In re* DDAVP Direct Purchaser Antitrust Litigation and *In re* DDAVP Indirect Purchaser Antitrust Litigation, No. 05-CV-2237 (CLB) (S.D.N.Y.) (order filed Nov. 2, 2006).

[166] *Id.*

[167] *In re* DDAVP Direct Purchaser Antitrust Litigation, appeal docketed No. 06-5525-CV (2d Cir. Dec. 15, 2006). Briefing was completed on August 1, 2007.

[168] For example, Eli Lilly obtained rights to U.S Pat. No. 4,971,998 "Methods for treating the premenstrual or late luteal phase syndrome" as applied to fluoxetine hydrochloride, the active ingredient in Prozac. Lilly then packaged and marketed a separate product "Sarafem" based on the method of use.

[169] The Hatch-Waxman Act allows an ANDA applicant to submit a "section (viii)" statement to the FDA whenever a patent listed in the FDA's Orange Book claims a method of using the listed drug and the applicant is not seeking approval for that claimed use. *See* 21 U.S.C. § 355(j)(2)(A)(viii).

[170] 91 F.3d 1493 (D.C. Cir. 1996).

Appeals for the District of Columbia held that the FDA may approve an ANDA even though the label of the generic product will not include one or more indications of the corresponding NDA.[171] Therefore, if a brand-name holder wishes to completely block generic competition for the new indication, the holder must create a new NDA and list the new method of use patent in the Orange Book.[172]

To increase the financial advantage of a "new indication" patent, some drug companies have attempted to assert patent protection rights outside the scope permitted by the FDA and the PTO. For example, Neurontin, originally protected by a patent for the anhydrous form of gabapentin, was also covered by a separate method patent for the treatment of epilepsy, which was due to expire in 2000.[173] In 1997, Warner-Lambert listed another method patent in the Orange Book, describing "novel methods for treating neurodegenerative diseases" including Alzheimer's, Parkinson's, Huntington's and ALS.[174] However, the FDA never approved gabapentin for those indications.[175]

In 1998, Purepac submitted an ANDA for generic gabapentin for the treatment of epilepsy.[176] The application included a "section viii statement"[177] to the effect that Purepac intended to market gabapentin only for epilepsy and not for any use claimed by the new neurodegenerative disease patent.[178] About a month later, TorPharm, Inc. also filed an ANDA, seeking permission to market

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[171] *Id.* at 1499–1501.

[172] For example, Sarafem is the same drug as Prozac (i.e., fluoxetine hydrochloride), with patent protection based on its indication for premenstrual syndrome. Both brands share the same NDA, NDA 01-8936, with different indications on the labeling approved by brand name.

[173] *Compare* U.S. Patent No. 4,087,544 (filed Apr. 28, 1977), *and* U.S. Patent No. 4,024,175 (filed Dec. 31, 1975) (covering the anhydrous form of gabapentin, including the pharmacologically compatible salts, expired in 1998), *with* U.S. Patent No. 4,087,544 (filed Apr. 28, 1977) (claiming that using gabapentin to treat certain forms of epilepsy, faintness attacks, hypokinesia, and cranial traumas expired in 2000).

[174] U.S. Patent No. 5,084,479 (filed Nov. 23, 1990).

[175] Purepac Pharmaceutical Co. v. Thompson, 238 F. Supp. 2d 191, 197 (D. D.C. 2002).

[176] *See* Purepac Pharm. Co. v. Thompson, 354 F.3d 877, 881 (D.C. Cir. 2004).

[177] Federal Food, Drug, and Cosmetic Act, §§ 505(j)(2)(A)(vii)(IV), (j)(2)(A)(viii), 21 U.S.C. §§ 355(j)(2)(A)(vii)(IV), (j)(2)(A)(viii) (2007). "An abbreviated application for a new drug shall contain–(viii) if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use."

[178] Purepac Pharm. Co., 354 F.3d at 881.

generic gabapentin. TorPharm submitted both a Paragraph IV certification and a section viii statement regarding the new patent.[179] In the course of ensuing litigation, the FDA recognized that the new patent had been improperly listed because it covered an unapproved use.[180] The FDA requested and received consent from Warner-Lambert's successor, Pfizer, to "delist" the patent from the Orange Book.[181]

Individual and class action lawsuits filed against Warner-Lambert and Pfizer alleged that their patent infringement litigation against the ANDA filers constituted sham litigation.[182] In August 2002, seventeen class action antitrust cases were consolidated for coordinated pretrial proceedings in the District of New Jersey, where the underlying patent litigation was pending.[183] Further proceedings were stayed, pending the outcome of the patent litigation.[184]

IV. SUGGESTED IMPROVEMENTS

The substantial information gap between the PTO and the FDA creates ample opportunity for abuse. The PTO has no authority to consult with the FDA before approving a patent.[185] Although the FDA recently revised its patent submission and listing processes to align its requirements more closely to PTO standards in an effort to staunch listing abuses, ultimately the FDA does not conduct any analysis of the patent itself.[186] The patent holder remains free to uni-

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[179] *Id.*

[180] *Id.* at 882.

[181] *Id.* Letter from Gary Buehler, Dir., Office of Generic Drugs, Ctr. for Drug Evaluation & Research, to ANDA Applicants for Gabapentin, *available at* http://www.fda.gov/cder/ogd/75350.479pat.pdf (Jan. 28, 2003).

[182] *See, e.g.*, Owens v. Pfizer, Inc., No. 2:02-1390 (D. N.J. 2002).

[183] *See In re* Gabapentin Patent Litigation (MDL-1384); *In re* Neurontin Antitrust Litigation, 217 F. Supp. 2d 1380 (J.P.M.L. 2002).

[184] *Id*.

[185] *See* 35 U.S.C. §§ 100–130. A patent applicant asserts utility by establishing that a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention and that the utility is specific, substantial, and credible. *Id*. at §§ 101, 112, first paragraph; MPEP § 2107 (8th ed., rev. Aug. 2006). "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (e.g., test data, affidavits or declarations from experts in the art, patents or printed publications) that is probative of the applicant's assertions." MPEP § 2107 (8th ed., rev. Aug. 2006).

[186] Applications for FDA Approval to Market a New Drug, 68 Fed. Reg. 36,676 (June 18, 2003) (codified at 21 C.F.R. § 314).

laterally certify its legal right to list the patent.[187] The flawed system that prevents the FDA and the PTO from consulting each other on listing matters facilitates the types of abuses outlined in this paper. Better interaction between the two regulatory bodies would provide a starting point, for example, in preventing pharmaceutical companies from taking inconsistent positions before the PTO and the FDA, as Bristol-Myers Squibb was alleged to have done with BuSpar.[188] Thus, if an NDA holder asserts that the scope of the patent covers the drug submitted for listing in the Orange Book, and that assertion is challenged by a third party, the FDA could send the matter to the PTO examiner to verify that the drug reads on the patent and has not been carved out through the prosecution history. Similarly, if the patent application alleges specific pharmaceutical utility of a drug, and a third party challenges the utility, the PTO could send the application to the FDA for verification. This might have solved the problems raised by AstraZeneca's roll-out of Nexium.[189]

Additionally, just as Hatch-Waxman invoked a compromise between protecting intellectual property rights and encouraging generic competition,[190] additional legislation is necessary to clarify the extent to which a brand-name manufacturer may block generic competition by reformulating its products. Congress, therefore, should reassess the appropriate balance between: (1) an innovator's right to remove a safe and effective product from the marketplace, and replace it with a "new and improved" version of the drug; and (2) consumers' interest in access to affordable versions of the discontinued product. Under current FDA regulations, an ANDA applicant cannot reference an NDA once it has been removed from the Orange Book.[191] One possible option is a statutory prohibition against removing national drug data codes or other essential pharmaceutical reference numbers in order to preserve generic substitution, at least for some reasonable period of time. The ANDA applicant could also reference the clinical research of an approved NDA. This

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[187] The FDA has made clear that patent review is outside its purview. *Id.* at 36,678; 21 C.F.R. § 314.53(f); *see* Apotex Inc. v. Thompson, 347 F.3d 1335, 1349 (Fed. Cir. 2003) (FDA not required to review patents listed in Orange Book).

[188] *See supra* notes 85–95 and accompanying text.

[189] *See, e.g., In re* Buspirone Antitrust Litig., 185 F. Supp. 2d, at 356–57 (S.D.N.Y. 2002); *see* discussion *supra* III.A.1.

[190] *See* H.R. REP. NO. 98-857 (I), at 14–15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2647–48. ([P]urposes are "to make available more low cost generic drugs" and "to create a new incentive for increased expenditures" for research and development of patented drugs.).

[191] 21 C.F.R. § 314.94(a)(3)–(4).

would not infringe on a brand-name company's right to innovate, patent, and exploit new discoveries.

A rational proposal for improvement necessarily requires both legislative and judicial action. If a patent holder improperly submits a patent for listing in the Orange Book, the only recourse a generic competitor has is to file an ANDA and wait for an infringement challenge.[192] Currently, there is no private cause of action challenging the appropriateness of the listing,[193] but there should be. Even under the amended Hatch-Waxman Act, brand-name pharmaceutical companies are able to file questionable infringement actions and invoke the Act's thirty-month stay.[194] This delays generic entry regardless of the merits of the patent litigation.

Hatch-Waxman provides that the FDA may grant approval of an ANDA before the thirty-month stay has run its course if the patent is held invalid or not infringed.[195] In an FTC study, the average time between the filing of a patent infringement lawsuit and a district court decision in the case was twenty-five months and thirteen days, and the time between the filing of a patent infringement lawsuit and a court of appeals decision in the case was thirty-seven months and twenty days.[196] In *Markman v. Westview Instruments, Inc.*, the U.S. Supreme Court determined that claim construction interpretation is a question of law for the district court judge rather than a question of fact for the jury, even though the interpretation of patent claims may include the interpretation of some factual material.[197] Since claim construction is a legal, rather than factual, determination, a party can move for a hearing before the judge prior to trial in order to construe the meaning of the patent claims.[198] In

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[192] *See* Teva Pharm. USA, Inc. v. Pfizer Inc., 395 F.3d 1324, 1324 (Fed. Cir. 2005) (no "reasonable apprehension of imminent suit"). *But see* Teva Pharm. USA, Inc. v. Novartis Pharm. Corp., 482 F.3d 1330 (Mar. 30, 2007) (where patent holder sued on one patent, ANDA filer could sue on rest) (expressly relying on Medimmune Inc. v. Genentech, 127 S.Ct. 764 (2007) (patent licensee need not terminate license agreement before seeking declaratory judgment concerning patent validity)).

[193] Mylan Pharm., Inc. v. Thompson, 268 F.3d at 1330–33. The Federal Food, Drug, and Cosmetic Act creates no private right of action. 21 U.S.C. §§ 301–99 (2007).

[194] *See, e.g.*, FTC, *Wrongful* "*Orange Book*" *Listing Raises Red Flag with FTC*, http://www.ftc.gov/opa/2002/04/biovailtiazac.htm (Apr. 23, 2002).

[195] 21 U.S.C. § 355(j)(5)(B)(iii).

[196] FED. TRADE COMM'N, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY (2002), *available at* http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf (last visited Sept. 12, 2007).

[197] Markman v. Westview Instruments, 52 F.3d 967 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996).

[198] *Id.* at 980.

some cases, merely construing the meaning of the claims during a pre-trial hearing is sufficient to end infringement litigation.[199] For example, during *In re Buspirone*, while ANDA filers Mylan and Watson moved for summary judgment on the grounds that their manufacture and sale of generic BuSpar did not infringe BMS's patent, BMS requested the *Markman* hearing on claim construction.[200] Less than fifteen months after BMS filed the patent with the FDA, Mylan's and Watson's motion for summary judgment on the infringement case was granted, and Judge John G. Koeltl held the BMS patent did not cover uses of buspirone, effectively ending litigation.[201]

Currently, the use of Markman hearings is not without problems, however.[202] The Supreme Court decision in *Markman* did not prescribe the actual way judges should reach decisions on construction.[203] Nor did the Court provide any specific timing for holding *Markman* hearings.[204] Consequently, the district courts have implemented *Markman* hearings inconsistently and reversal rates on appeal are high.[205] Reform initiatives, including consistent use of *Markman* hearings early in litigation, guidelines for reaching construction decisions, and interlocutory appeals, hold promise for improving the efficiency and effectiveness of *Markman* hearings.[206]

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[199] *See In re* Buspirone, MDL No. 1410, slip op. at 6–26 (S.D.N.Y. Feb. 14, 2002) (Order No. 18) (Motion for Summary Judgment on Patent Infringement Claims).

[200] *In re* Buspirone, 185 F. Supp. 2d 340, 351–52 (S.D.N.Y. 2002) (Order No. 18) (Motion for Summary Judgment on Patent Infringement Claims). The court concluded that the patent did not cover the generics' uses of buspirone based on claim construction, the language of the specification, and prosecution history (or in the alternative, based on 35 U.S.C. § 102(b)). *Id*. at 355–59.

[201] *Id.* at 363. The decision issued on February 14, 2002.

[202] *See* Mark R. Malek, *Markman Exposed: Continuing Problems With Markman Hearings*, 7 U. FLA. J.L. & PUB. POL'Y 195 (2002)

[203] Markman v. Westview Instruments, 52 F.3d 967 (Fed. Cir.) (en banc), *aff'd*, 517 U.S. 370 (1996).

[204] *Id.*

[205] *See* Kimberly A. Moore, *Markman Eight Years Later: Is Claim Construction More Predictable?*, 9 LEWIS & CLARK L. REV. 231, 236–39 (2005) (finding between the 1996 Markman decision and 2003, the Federal Circuit reversed 40.8% of cases if summary affirmances were excluded, reversed 34.51% if summary affirmances were included and reversed 37.5% in cases in which the Federal Circuit held one or more patent claims wrongly construed).

[206] *See* THE SEDONA CONFERENCE, REPORT OF THE SEDONA CONFERENCE WORKING GROUP ON THE MARKMAN PROCESS (Public Comment Version 2006), http://www.thesedonaconference.org/content/miscFiles/6_06WG5pubcomment.pdf, ("The Sedona Conference is a nonprofit, 501(c)(3) research and educational institute dedicated to the advanced study of law and policy in the areas of antitrust law, complex litigation, and intellectual property rights.").

Court decisions are currently in disarray in their treatment of pharmaceutical patents.[207] Some courts disregard the effect that the Hatch-Waxman Act has on the balance between patent and antitrust law.[208] The nature of research and development in the pharmaceutical industry spawns large numbers of questionable patents.[209] Moreover, the price differential between brand-name and generic drugs significantly affects industry profits, encouraging abuse.[210] Yet no efficient mechanism exists for challenging these abuses. Antitrust litigation is slow, cumbersome, and expensive.[211] Results can be unpredictable.[212]

The Supreme Court has thus far declined to review any pharmaceutical antitrust cases, most recently denying *certiorari* in *FTC v. Schering-Plough Corp*.[213] and in *Joblove v. Barr Labs*.[214] A number of "switching" cases are moving up to the appellate courts, and there is likely to be much confusion concerning reformulation and life cycle management. Courts are loathe to carve out special antitrust rules for particular industries. However, in the case of the pharmaceutical

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[207] *See* George G. Gordon, A Summary of Recent Pharmaceutical Cases Raising Intellectual Property-Antitrust Issues, ABA Antitrust Section Spring Meeting (Mar. 30, 2005).

[208] *See, e.g., In re* DDAVP Direct Purchaser Antitrust Litigation and *In re* DDAVP Indirect Purchaser Antitrust Litigation, No. 05-CV-2237 (CLB) (S.D.N.Y.) (order filed Nov. 2, 2006) (Ferring's suit was standard response to Hatch-Waxman, not a sham); Schering-Plough Corp. v. FTC, 402 F.3d 1056 (11th Cir. 2005) (payments from patent holder to alleged infringer were a natural consequence of Hatch-Waxman).

[209] *See* NAT'L INST. FOR HEALTH CARE MGMT., CHANGING PATTERNS OF PHARMACEUTICAL INNOVATION 5 (2002), http://www.nihcm.org/innovations.pdf. *But see* PhRMA, NIHCM'S report on Pharmaceutical Innovation: Fact vs. Fiction, *available at* http://mednet3.who.int/prioritymeds/report/append/8342.pdf (June 11, 2002).

[210] *See, e.g.*, C. Scott Hemphill, Paying for Delay: Pharmaceutical Patent Settlement as a Regulatory Design Problem, 81 N.Y.U. L. REV. 1553 (2006). *Cf.* John Carreyrou, *Inside Abbott's Tactics to Protect AIDS Drug*, WALL ST. J., Jan. 3, 2007, at A1.

[211] The cost of antitrust litigation contrasts sharply with the relative ease with which pharmaceutical companies can presently make false Orange Book filings or initiate a sham patent infringement case. *See* Susan A. Creighton, et al., *Cheap Exclusion*, 72 ANTITRUST L.J. 975, 983–84 (2005).

[212] *Compare, e.g.,* Valley Drug Co. v. Geneva Pharm., Inc., 344 F.3d 1294 (11th Cir. 2003), *with In re* Cardizem CD Antitrust Litig., 332 F.3d 896 (6th Cir. 2003). Patent cases can also be unpredictable. For an empirical analysis of the role of juries in patent cases and win rates by substantive issues tried, see Kimberly A. Moore, *Judges, Juries, and Patent Cases - An Empirical Peek Inside the Black Box*, 99 MICH. L. REV. 365 (2000).

[213] 126 S. Ct. 2929, 2929 (2006).

[214] 127 S. Ct. 3001 (2007) (*cert. denied* on June 25, 2007). The question presented in the petition for certiorari was, "under what circumstances is an agreement by a brand pharmaceutical manufacturer (and patent holder) to share a portion of its future profits with a generic market entrant (and alleged patent infringer), in exchange for the generic's agreement not to market its product, a violation of the antitrust laws?"

industry, specialized laws and regulations already govern production, marketing, and sales of prescription and over-the-counter drugs.[215] The Supreme Court should clarify that abuses of PTO and FDA processes can form the basis for antitrust treble damage liability to consumers, as well as to generic drug manufacturers. While patents reward innovation, the threat of antitrust damages should deter abuses.

V. CONCLUSION

Although recent legislative reforms have sought to restrict abuse of FDA and PTO processes, the reforms rely too much on the good will of the parties involved rather than on effective and proactive controls. Congress must mandate better communication between the FDA and the PTO, requiring each agency to defer to the expertise of the other when issues of abuse arise during NDA/ANDA applications, patent prosecutions, or patent listings. Judicially, the use of *Markman* hearings holds promise for accelerating ANDA approvals, but the Court of Appeals for the Federal Circuit and the United States Supreme Court must also address the legal issues surrounding pharmaceutical reformulation. Legislative and adjudicatory reconciliation of current tensions between intellectual property law and antitrust law is sound public policy. Patents stimulate pharmaceutical innovation, but unjustified extensions of patent protections stifle true medical progress and increase the cost of health care. If lack of competition drives prices too high, consumers unable to afford critical medications face potentially deadly consequences. Reform of the laws governing life cycle management is imperative.

[215] *See* Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301–360.