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Symposium: Molecules and Conflict: Cancer, Patents, and Women's Health

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MOLECULES AND CONFLICT: CANCER, PATENTS, AND WOMEN'S HEALTH

EILEEN M. KANE*

Effective health care for women relies on a nexus of scientific, medical, and legal regimes. Intellectual property law offers incentives for creative accomplishments, and patent law, in particular, offers incentives for the development of medical innovations. This Article examines an intersection of women's health and the patent system. Breast cancer is the most common cancer in women and has been the focus of sustained basic and clinical scientific research. The Article presents an analysis of patent-related issues that have accompanied the development of leading compounds for the prevention, diagnosis, and treatment of breast cancer, in particular, Taxol, Tamoxifen, Herceptin, and the BRCA1 and BRCA2 genes. Collectively, these molecules track the intellectual development of the breast cancer research field. As a result, the patent issues range from those that arise in a mature pharmaceutical market to those that can only emerge from new advances in biotechnology.

Through the lens of a specific disease-centered analysis, paradigmatic conflicts related to pharmaceutical patents are illustrated here: the management of public-private technology transfer efforts between government and industry, and the intellectual property conflicts that can arise over an unpatentable compound (Taxol); initiatives to accelerate generic pharmaceutical development and the antitrust concerns raised by collusion between brand-name and generic pharmaceutical companies in

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patent settlements (Taxol, Tamoxifen); the resolution of patent rights to novel molecular targets between competing biotechnology companies, and the demand for the establishment of a regulatory pathway for biogenetics (Herceptin); the controversy over the patenting of DNA, especially genes, and whether such patent rights interfere with scientific progress or reduce clinical access, and the contrasting opportunities for public opposition between the American and European patent systems (BRCA1 and BRCA2 genes). The efforts of women's health advocates to intervene where patent-related obstacles complicate patient access to therapeutic compounds can be observed at many of these junctures.

The women's health movement of the last several decades has focused attention on the health care needs of women, particularly with respect to gender-specific diseases, such as breast cancer. Increased biomedical research into women's health, a desirable outcome of such activism, may be accompanied by patent-related issues that paradoxically frustrate access to medical breakthroughs. A comprehensive effort to ensure women's access to health resources must incorporate an analysis of patent incentives for research and development as well as patent-related barriers to medical treatment in order to guarantee gender parity in health care.

Introduction	306
II. Taxol	310
III. Tamoxifen.....	318
IV. Herceptin	323
V. BRCA1 and BRCA2 Genes.....	328
Conclusion.....	333

INTRODUCTION

Effective health care for women relies on a nexus of scientific, medical, and legal regimes. Intellectual property law offers incentives for creative accomplishments, and patent law, in particular, offers incentives for the development of medical innovations. This Article will examine an intersection of patent law with women's health issues. Breast cancer is a leading cause of mortality for women in the United States. In 2005, the American Cancer Society estimated that 212,920 women would be

diagnosed with breast cancer and 40,970 women will die of the disease.¹ In the last decade or so, there has been increased attention to this disease by women's health activists. This focus can be traced to the medical toll that the disease has taken on the lives of women, but the phenomenon also represents a maturing of the women's health movement in the last several decades that has galvanized public interest in women's health, particularly with respect to often neglected gender-specific diseases.² In general, the modern biomedical climate is shaped by significant advocacy from patients organized into disease-specific constituencies, which aim to increase private and public research funding through sustained lobbying efforts.³

In its most basic sense, cancer is a cellular disease in which normal cell replication accelerates, resulting in tumor formation.⁴ Cancers are initially classified by their site of appearance, such as lung, breast, or colon. While cancer cells in general share common biochemical characteristics, each specific type of cancer has individualized properties and requires focused attention. Thus, much of cancer research is organized into studies that concentrate on a particular cancer, and funding sources often specify a cancer of interest in the allotment of resources.⁵ Progress in medical research is often accompanied by the patenting of specific advances, whether new drugs or treatment methods, and the breast cancer field is no exception.

The government grant of a patent confers specific rights upon the holder to exclude others from making, using, or selling the invention.⁶

1. American Cancer Society Statistics, <http://seer.cancer.gov/statfacts/html/breast.html> (last visited Nov. 30, 2006).

2. Dr. Bernadine Healy, as Director of the National Institutes of Health (NIH), created the Office of Research on Women's Health in 1990 and established the Women's Health Initiative to ensure gender equity in the research on and treatment of women's health issues. See Londa Schiebinger, HAS FEMINISM CHANGED SCIENCE? 123 (1999) (giving a thorough treatment of the integration of women's health issues into American medicine). The Food and Drug Administration created an Office of Women's Health to specifically monitor gender equity in pharmaceutical research. See Londa Schiebinger, *Women's Health and Clinical Trials*, 112 J. CLIN. INVEST. 973 (2003) (describing historic underrepresentation of women from clinical trials of new pharmaceuticals).

3. Breast cancer advocacy, evidenced by the emergence of specific organizations such as the National Breast Cancer Coalition, Breast Cancer Action, Susan G. Komen for the Cure, and Y-Me, is an example of disease-centered patient advocacy. For a history of breast cancer patient activism (and referencing the earlier models provided by AIDS activists), see MAUREEN HOGAN CASAMAYOU, *THE POLITICS OF BREAST CANCER* (2001).

4. See BRUCE ALBERTS ET AL., *THE MOLECULAR BIOLOGY OF THE CELL* 1313-61 (2002) (describing the molecular basis of cancer cell biology, and the opportunities for clinical intervention based on a detailed biochemical comparison between normal and cancer cells).

5. See National Cancer Institute, Cancer Research Portfolio, <http://research.portfolio.cancer.gov> (last visited Nov. 30, 2006) (organizing federal cancer research by specific cancers, and listing 2,128 funded breast cancer research projects directed to treatment, prevention, detection, survivorship, etiology, biology, and scientific model systems).

6. 35 U.S.C. § 154 (2006). The grant consists of "the right to exclude others from

Patentability turns on the satisfaction of criteria that can be conceptually divided into two groups: those that apply to the invention and those that concern the sufficiency of the patent application itself. The invention itself must satisfy the requirements for patentable subject matter,⁷ utility,⁸ novelty,⁹ and nonobviousness.¹⁰ The written patent document (the specification) must meet separate legal requirements for the adequacy of the disclosure itself.¹¹ The patent examination process conducted by the United States Patent and Trademark Office (PTO) is intended to result in the grant of patents that have met all of these requirements, and, as a result, an issued patent enjoys a presumption of validity.¹² Nonetheless, these statutory grounds for patentability can resurface in patent litigation. An accused infringer can later allege that an issued patent is invalid for failure to satisfy one of these statutory criteria. The patent holder faces the possibility of a judgment of patent invalidity in litigation, illustrating the potential vulnerability of a patent asserted against accused infringers.¹³

The pharmaceutical industry, which often mediates the transfer of basic scientific research into commercial drug products, has relied extensively on patents and the resulting market exclusivity that can be achieved during the patent term. In this sense, patent protection offers an incentive to undertake scientific research. The industry expects that significant financial returns from the marketplace will fund the research and development (R&D) of new drugs and finance the clinical trials that are necessary in order to win the approval of the Food and Drug Administration (FDA) for marketing.¹⁴ Industry claims about the high cost

making, using, offering for sale, or selling the invention throughout the United States or importing the invention into the United States, and, if the invention is a process, of the right to exclude others from using, offering for sale or selling throughout the United States, or importing into the United States, products made by that process." *Id.* A patent term is twenty years from the date of the filing of the patent application. *Id.* The origin of the U.S. patent system can be traced to the U.S. Constitution, Article 1, Section 8, authorizing Congress to develop a system "[t]o promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries." U.S. CONST. art. 1, § 8, cl. 8.

7. 35 U.S.C. § 101 (2006). A patent may be granted for a process, machine, manufacture or composition of matter. A drug compound is a composition of matter.

8. *Id.* The invention must be useful, as defined by the inventor.

9. 35 U.S.C. § 102 (2006). A patent is barred by any public disclosure of identical subject matter.

10. 35 U.S.C. § 103 (2006). An invention may not be patented if its subject matter would be obvious to one of ordinary skill in the art.

11. 35 U.S.C. § 112, 1st paragraph (2006). The patent document is required to have certain attributes, including enablement, written description, and best mode, so that the invention is fully disclosed.

12. 35 U.S.C. § 282 (2006).

13. Because a patent issued by the PTO is considered valid, the evidentiary standard for a defendant to prove invalidity is clear and convincing evidence.

14. See Rebecca S. Eisenberg, *The Shifting Balance of Patents and Drug Regulation*, 20

of drug development have been criticized, with some critics claiming that a disproportionate amount of revenue is directed to the marketing and promotion of drugs, rather than to research.¹⁵ Pharmaceutical patents are a type of chemical patent, and patents may be separately obtained for various aspects of the underlying invention: drug compound, method of use, formulation, and synthetic process. Drug substance patents cover the active ingredient in the pharmaceutical product, while a method of use patent can cover the use of the product to treat a specific condition.¹⁶ The potential for a pharmaceutical company to hold multiple patents related to a particular drug product can ensure a dominant position in the market.

The Article will survey intellectual property issues that have arisen in the breast cancer field, specifically focusing on patent conflicts over specific molecules with medical significance for the prevention, diagnosis, and treatment of breast cancer: Taxol, Tamoxifen, Herceptin, and the BRCA1 and BRCA2 genes. This disease-centered analysis of patent issues is also broad: the breast cancer patent climate illuminates many of the types of patenting disputes that are paradigmatic in modern pharmaceutical science. The case study of Taxol in Part II has implications for effective government stewardship of its biomedical enterprise. The unavailability of patent protection for an anticancer compound has not precluded intense conflicts over other kinds of intellectual property claims and proprietary disputes, as discussed in Part II with respect to Taxol. The recurring conflicts between brand-name and generic pharmaceutical companies over the rights to market and sell high profile treatments emerge in this narrative, with accompanying antitrust concerns, as illustrated in Part II and Part III with respect to Taxol and Tamoxifen. As breast cancer research moved into the age of molecular biology, more recent controversies over the patenting of biotechnology products appear. The patenting disputes over Herceptin, a monoclonal antibody, and the BRCA1 and BRCA2 genes illustrate these dilemmas. Herceptin demonstrates the need for the development of a generic approval process for medicines derived from biotechnology, and the BRCA1 and BRCA2 patents raise questions regarding the management of patents to genomic inventions. Significant

HEALTH AFFAIRS 119, 120 (2001).

15. The most widely industry-cited estimate is that a new drug costs about \$800 million to bring to market. This figure emerges from the largely industry-funded Tufts Center for the Study of Drug Development study. See Joseph A. DiMasi et. al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151 (2003). But see MARCIA ANGELL, THE TRUTH ABOUT DRUG COMPANIES 41-49 (2004) (giving a critical analysis of the validity of DiMasi's study, noting in particular that the study used figures provided by the pharmaceutical companies that could not be independently verified and only accounted for the most expensive drugs). Dr. Angell is the former editor in chief of the NEW ENGLAND JOURNAL OF MEDICINE. *Id.*

16. See JOHN R. THOMAS, PHARMACEUTICAL PATENT LAW 38-39, 44-49 (2005).

differences between the United States and Europe in the availability of patent opposition procedures are illustrated by the legal challenges posed to the European patents on the BRCA1 and BRCA2 genes. Finally, breast cancer activism by organizations exclusively devoted to education, advocacy, and support for the disease has included efforts to address patent-mediated obstacles to the availability of medical treatments. As the Article will demonstrate, the conflicts over pharmaceutical access can involve three separate areas of the law: patent, food and drug, and antitrust law.

The molecules that are the focus of the Article follow from the evolution of modern cancer research: the science of oncology has progressed from employing undifferentiated attacks on tumors to designing precise molecular treatments based on detailed structural knowledge of the cancer cell in specific cancers.¹⁷ The traditional modalities of surgery, radiation, and chemotherapy have been supplemented or replaced with targeted approaches identified through molecular biology.¹⁸ The Article analyzes the patent issues with respect to Taxol, Tamoxifen, Herceptin, and the BRCA1 and BRCA2 genes, critical compounds for the prevention, diagnosis, and treatment of breast cancer, considering the role of patents as incentives for research and the role of patents in mediating patient access to these medical advances.

II. TAXOL

Cancer cells exhibit a characteristic disorder—they do not observe the routine cell cycle that regulates when cells divide. Their growth is unchecked and off-cycle; the processes of cell replication accelerate, resulting in tumor formation. In order to divide so rapidly, the cancer cell must organize its cellular machinery to facilitate rapid cell division. This fact can be exploited by researchers—any disruption of the required cellular machinery will interfere with the unchecked growth of these cells.

There is a lengthy history of federal investment in cancer research and pharmaceutical development. The National Cancer Institute (NCI) is an institute within the National Institutes of Health (NIH) and was established

17. See SUSAN M. LOVE, M.D. & KAREN LINDSEY, DR. SUSAN LOVE'S BREAST BOOK 244 (2005) ("[W]e have seen the approach to treating breast cancer shift from surgery center stage and radiation and chemotherapy playing supporting roles, to chemotherapy and hormone therapy as the leads while surgery and radiation have moved into ancillary positions.").

18. A phrase from Dr. Susan Love summarizing traditional approaches to cancer treatment as "slash, burn, and poison" has been quoted often in the medical literature. See ROBERT BAZELL, *HER 2: THE MAKING OF HERCEPTIN, A REVOLUTIONARY TREATMENT FOR BREAST CANCER* 25 (1998).

in 1937 with the passage of the National Cancer Act.¹⁹ The NCI established the Natural Products Program in 1958 to screen 35,000 plant species for compounds that might exhibit anticancer activity.²⁰ An extract from the bark of the Pacific yew tree showed antitumor activity. One such compound from the plant was isolated in 1971 and was given the name Taxol.²¹ The mechanism by which Taxol could arrest the proliferation of cancer cells was elucidated by Susan Horwitz and her colleagues, who discovered that the compound prevented the formation of microtubules, disrupting the cellular apparatus required for cell division.²² This mechanism is a general one—meaning that many different types of cancer cells might be receptive to this interruption.²³ In practice, however, such agents will usually demonstrate particular efficacy against specific cancers that cannot be predicted in advance.

The NCI filed an Investigational New Drug Application (IND) with the FDA to begin clinical trials of Taxol in 1983.²⁴ Phase II trials began in 1985.²⁵ NCI, as a federal research institute, however, could not undertake the development of the compound as a pharmaceutical.

It is important to note that Taxol was not a patentable compound. At the time that its clinical potential was recognized for the treatment of cancer, the compound had been known in the scientific community for many years and had been characterized in the scientific literature. As a result, the compound could not meet the novelty requirement of U.S. patent law and was in the public domain.²⁶ Other forms of patent protection remained available, however, such as patents on the process of making or using the compound or patents to specific pharmaceutical formulations of the compound. Patents of methods using a compound in specific clinical applications may have commercial potential.²⁷

19. CASAMAYOU, *supra* note 3, at 27-29 (describing the origin of efforts to involve the federal government in cancer research, which led to the establishment of the National Cancer Institute).

20. UNITED STATES GENERAL ACCOUNTING OFFICE, GAO-03-829, TECHNOLOGY TRANSFER: NIH-PRIVATE SECTOR PARTNERSHIP IN THE DEVELOPMENT OF TAXOL 8-9, 2003 [hereinafter GAO REPORT].

21. *Id.* at 4 (noting that Taxol is also the trademarked brand name chosen by Bristol-Myers Squibb, while the generic name is paclitaxel).

22. Peter B. Schiff and Susan Band Horwitz, *Taxol Stabilizes Microtubules in Mouse Fibroblast Cells*, 77 PROC. NATL. ACAD. SCI. 1561 (1980).

23. ALBERTS ET AL, *supra* note 4, at 928.

24. GAO REPORT, *supra* note 20, at 9.

25. *Id.* at 9.

26. See 35 U.S.C. § 102 (2006); GAO REPORT, *supra* note 20, at 32.

27. See Rebecca S. Eisenberg, *Pharmaceutical Innovation and Cost: American Dilemma: The Problem of New Uses*, 5 YALE J. HEALTH POL'Y & ETHICS 717, 724 (2005) (noting, however, the difficulties in the enforcement of therapeutic method claims).

In the 1970s, Congress had recognized that the results of federally funded research often did not get transferred for commercial development in the absence of explicit mechanisms to involve the private sector.²⁸ Legislative action began with the enactment of the Stevenson-Wydler Act in 1980, which authorized federal agencies to “transfer federally owned or originated technology to State and local governments and to the private sector.”²⁹ This original imperative was strengthened with the enactment of the Federal Technology Transfer Act of 1986.³⁰ These statutes authorize government laboratories to enter into cooperative research and development agreements (CRADAs) with industrial partners in order to facilitate technology transfer from government to the private sector.³¹ These efforts begin with the publication of a notice in the Federal Register that announces the CRADA opportunity.³²

In 1989, NIH published a CRADA notice seeking an industrial partner to develop Taxol for entry into the market.³³ Four applications were received, and the NIH chose Bristol-Myers Squibb (BMS) as its CRADA partner.³⁴ The signing of this agreement led to an exchange whereby NCI would provide its clinical trial data to BMS for use in its New Drug Application (NDA) to the FDA, while BMS would supply NCI with quantities of Taxol for use in its studies.³⁵ In 1992, BMS received FDA approval for the use of Taxol in the treatment of refractory ovarian cancer, and in 1994, it received approval for Taxol use in the treatment of advanced breast cancer.³⁶

The absence of patent protection for the Taxol compound did not foreclose other means by which BMS could maintain exclusive control of the Taxol market. The CRADA agreement gave BMS the exclusive use of

28. See, e.g., Rebecca S. Eisenberg, *Public Research and Private Development: Patents and Technology Transfer in Government-Sponsored Research*, 82 VA. L. REV. 1663 (1996) (describing the history of the efforts to recruit the private sector to the project of commercializing inventions resulting from federally funded research).

29. Stevenson-Wydler Technology Innovation Act of 1980, § 11, 94 Stat. 2311, 2318 (1980)(codified as amended at 15 U.S.C. § 3710 (a), (b) (2006)). The other significant mechanism for federal technology transfer was also created in 1980 by the Bayh-Dole Act, which allowed government grantees, such as universities, to retain title to their inventions and engage in their own efforts to commercialize such technologies. Pub. L. No. 96-517 § 6, 94 Stat. 3019 (1980) (codified as amended at 35 U.S.C. §§ 200-212 (2006)).

30. Federal Technology Transfer Act of 1986, Pub. L. No. 99-502, 100 Stat. 1785 (1986) (codified as amended at 15 § U.S.C. 3710(e) (2006)).

31. *Id.*

32. *Id.*

33. Opportunity for a Cooperative Research and Development Agreement (CRADA) for the Scientific and Commercial Development of Taxol as an Anticancer Agent, 54 Fed. Reg. 31,733 (1989).

34. GAO Report, *supra* note 20, at 9.

35. *Id.*

36. *Id.*

the clinical data gathered by NCI, and thus BMS was the only pharmaceutical company that was able to secure an FDA approval for Taxol. BMS was granted five years of market exclusivity by the FDA because Taxol was a new chemical entity (NCE) not previously approved by the FDA, a status that automatically triggers the award of such exclusivity by statute.³⁷

The anticipated end to BMS's market exclusivity in 1997 did not occur due to the company's activities in building a Taxol-related patent portfolio. As previously discussed, a patent may be filed on a particular method of making or using the compound, known as a method patent.³⁸ BMS filed for its own patents on various methods to use Taxol in cancer treatment, and two patents were issued.³⁹ Because Taxol itself was not under patent, the therapeutic market was of immense interest to generic pharmaceutical companies who were interested in bringing low-cost alternatives to market.⁴⁰ All possible generic entrants were required to observe any existing patents that might pertain to their proposed products, and this is where the BMS patent strategy showed force.

Some background information is required. By the 1980s, Congress recognized the need to incentivize the generic pharmaceutical industry, so that lower-cost alternatives to brand-name pharmaceuticals could be developed. In an effort to encourage the development of generic pharmaceuticals as alternatives to brand-name products, the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Act") was enacted with objectives that addressed the concerns of both brand-name and generic pharmaceutical companies.⁴¹ The statute accomplished several objectives. Brand-name pharmaceutical companies were offered patent term restoration when effective pharmaceutical patent terms had been eroded by clinical testing and FDA approval.⁴² A generic pharmaceutical company could rely on the safety and efficacy data provided by the brand-name pharmaceutical company when it sought FDA

37. See 21 U.S.C. § 355 (c)(3)(D)(ii), (iii) (2006).

38. See Eisenberg, *supra* note 27.

39. See U.S. Patent Nos. 5,641,803 (filed Oct. 18, 1995) (issued June 24, 1997) and 5,670,537 (filed Sept. 19, 1996) (issued Sept. 23, 1997) [hereinafter 1997 Patents].

40. A generic pharmaceutical is one with the same active ingredient as a brand-name pharmaceutical compound. A brand-name pharmaceutical has received first approval by the FDA for that active ingredient, and the public often associates the brand name with the active ingredient. The brand-name product commands dominant market position by virtue of its initial exclusivity. Patient loyalty may persist even after generic alternatives exist.

41. See Drug Price Competition and Patent Term Restoration Act of 1984, 98 Stat. 1585 (1984) (codified at 21 U.S.C. § 355 (2006), 35 U.S.C. § 156 (2006), and 35 U.S.C. § 271 (e) (2006)) (amending 21 U.S.C. §355(j)(2)(C) (2006)); see also THOMAS, *supra* note 16, at 12-19.

42. See 35 U.S.C. § 156.

approval for the original compound, as long as the generic compound was bioequivalent to the approved drug. The generic pharmaceutical manufacturer could then enter the market by filing an Abbreviated New Drug Application (ANDA) declaring its proposed generic compound to be bioequivalent to the existing approved product.⁴³ However, the generic pharmaceutical manufacturer is required to observe any existing patents covering the original product. This information can be obtained because the original filer of a New Drug Application (NDA) is required to inform the FDA of all patents that cover the pharmaceutical in question, and they are listed in an agency publication entitled “Approved Drug Products with Therapeutic Equivalence,” commonly known as the “Orange Book.”⁴⁴ In order to enter a market controlled by existing patents, a company seeking to develop a generic pharmaceutical is required to make one of four possible certifications and account for the relationship of its proposed pharmaceutical to the patents that are listed in the Orange Book.⁴⁵ The Hatch-Waxman Act also immunized generic pharmaceutical manufacturers from infringement claims based on activities undertaken to prepare for the filing of an ANDA.⁴⁶ The statute created specific procedures for the generic pharmaceutical applicant to challenge the validity of an existing pharmaceutical patent or for a patent holder to allege infringement in situations where an ANDA was filed with a Paragraph IV certification. The patent holder was granted an automatic 30-month stay upon the filing of an infringement suit against the ANDA filer in order for the infringement claim to be adjudicated.⁴⁷ The incentive for a generic pharmaceutical manufacturer to challenge an existing, possibly invalid patent was created by the award of a 180-day period of market exclusivity to the first generic applicant to file a patent challenge to an approved pharmaceutical.⁴⁸

The strategies used by BMS to maintain market monopoly following the expiration of its FDA-granted monopoly in 1997 relied on the questionable use of these Hatch-Waxman procedures, ultimately resulting in the filing of a Federal Trade Commission (FTC) Complaint alleging unlawful acts by

43. See 21 U.S.C. § 355(j)(2)(A)(iv).

44. See 21 U.S.C. § 355(j)(7)(A).

45. See 21 U.S.C. § 355(b)(2)(A)(i-iv). The generic applicant must certify that a patent pertaining to the proposed generic compound is (i) not filed; (ii) expired; (iii) the date on which such a patent will expire; or (iv) that such a patent is invalid or will not be infringed by the manufacture, use or sale of the new drug for which the application is submitted. *Id.* These certifications are generally denoted by their number in common parlance, such as a Paragraph IV certification.

46. See 35 U.S.C. § 271 (e)(1).

47. See 21 U.S.C. § 355(j)(5)(B)(iii).

48. See 21 U.S.C. § 355(j)(B)(iv).

BMS, which delayed generic competition in the Taxol market.⁴⁹ By 1997, BMS had two patents that could pose a barrier to generic entry into the Taxol market.⁵⁰ IVAX was the first company to file an ANDA. A patent infringement suit by BMS against IVAX triggered the statutory 30-month stay allowed by Hatch-Waxman. When litigation ensued, both BMS patents were found invalid, a decision upheld by the Federal Circuit.⁵¹ In its complaint, the FTC alleged that BMS obtained the method patents through inequitable conduct before the PTO and that BMS improperly listed the patents in the Orange Book.⁵² Although the patents were held invalid by 2001, the baseless litigation had succeeded in extending the BMS market monopoly.

The FTC further charged that BMS had licensed a third patent from American Biosciences, Inc. (ABI) and improperly listed the patent in the Orange Book in order to block or delay further attempts by generic competitors to enter the Taxol market.⁵³ This patent triggered a series of lawsuits that attempted to clarify the mechanisms for Orange Book listing, including whether a private right of action seeking an Orange Book listing is permissible under Hatch-Waxman.⁵⁴ The National Organization of Women (NOW) demanded that BMS halt its legal “manipulation of the judicial and regulatory systems in order to maintain its monopoly pricing.”⁵⁵ In response to the extensive uncertainty regarding the propriety of the Orange Book listing of this patent, the FDA did not require other generic ANDA applicants to certify to the patent, effectively removing this last patent as an obstacle to generic competitors.⁵⁶ As a result, the first

49. See Complaint, In re Bristol-Myers Squibb Co., No. C-4076 (F.T.C. Apr. 14, 2003), available at <http://www.ftc.gov/os/2003/03/bristolmyerscomp.pdf> [hereinafter FTC Complaint] (alleging anticompetitive conduct with respect to the drugs BuSpar, Taxol, and Platinol).

50. See 1997 Patents, *supra* note 39.

51. Bristol-Myers Squibb v. Ben Venue Labs, Inc., 246 F.3d 1368 (Fed. Cir. 2001).

52. FTC Complaint, *supra* note 49, at 7-18. Inequitable conduct refers to conduct by the patent applicant during patent prosecution in which material information is withheld from or misrepresented to the PTO in order to obtain a patent. See THOMAS, *supra* note 16, at 268-273.

53. *Id.* at 18-20 (citing U.S. Patent No. 6,096,331 as a separate source of anticompetitive competition).

54. See American Biosciences, Inc. v. Bristol-Myers Squibb Co., No. CB 00-08577-WMD AJWX, 2000 WL 1278348 (C.D. Cal. 2000) (noting BMS sought to voluntarily list the patent in the Orange Book after a court initially listed the patent by court order, which allowed ABI to sue IVAX for patent infringement, further delaying generic entry). Ultimately, the court decided that there was no private right of action to force the listing of a patent. *Id.*

55. Press Release, National Organization for Women, Feminists Demand Affordable Anti-Cancer Drug, Take on Pharmaceutical Manufacturer (Dec. 3, 2001), <http://www.now.org/press/12-01/12-03-01.html> (reporting monopoly pricing “as high as \$20,000 per patient per year,” partly due to loopholes in the Hatch-Waxman Act).

56. See FEDERAL TRADE COMMISSION, GENERIC DRUG ENTRY PRIOR TO PATENT

approval of generic Taxol to IVAX occurred in September 2000.⁵⁷ The FTC reached a settlement with BMS, with BMS agreeing not to enforce or collect royalties on any new “Taxol Patent” that could possibly cover the existing FDA-approved product, to refrain from any sham litigation to injure a generic competitor, and to avoid any improper Orange Book listings which would delay generic competition.⁵⁸ A separate class action suit against BMS on behalf of consumers filed by State Attorneys General, alleging fraudulent procurement of patents to delay generic competition, was settled in 2004, and a fund was established to provide payment to patients who effectively overpaid for Taxol.⁵⁹

The extensive litigation and Hatch-Waxman disputes over Taxol illustrate the potential for a brand-name manufacturer to manipulate complicated regulatory processes in order to maintain control of a lucrative pharmaceutical market. The conduct of BMS with respect to Taxol and other products was at least partly responsible for eliciting FTC attention and investigation into a wider pattern of anticompetitive conduct by brand-name drug companies to delay the development of competitive generic pharmaceuticals.⁶⁰ Subsequent amendments to the Hatch-Waxman Act, responding to perceived loopholes in the original enactment, now limit a pharmaceutical company to one 30-month stay of approval per ANDA application, limit the types of patents that may be listed in the Orange Book, allow for a generic company counterclaim requesting delisting of a patent in the Orange Book, and award the 180-day market exclusivity to a generic company only upon commercial marketing of a product.⁶¹

The phenomenal market success of Taxol drew attention to the proper management of technology transfer from the federal government to private

EXPIRATION: AN FTC STUDY A-37, July 2002 [hereinafter FTC REPORT].

57. *Id.*

58. See Federal Trade Commission Consent Order Analysis, *In re Bristol-Myers Squibb Co.*, <http://www.ftc.gov/os/2003/03/bristolmyersanalysis.htm> (last visited Nov. 30, 2006) (noting that BMS “abused governmental processes to delay generic competition” for several of its brand-name drugs, including Taxol).

59. Press Release, Office of the Attorney General (April 24, 2003), http://www.oag.state.ny.us/press/2003/apr/apr24b_03.html. (noting that the antitrust action was filed by all 50 states and resulted in a compensation fund established to reimburse patients who overpaid for Taxol between 1999 and 2003).

60. See FTC Report, *supra* note 56, at 1 (“The study was designed to determine whether...particular provisions of the Hatch-Waxman Amendments are susceptible to strategies to delay or deter consumer access to low-cost generic alternatives to brand-name products.”). The report recommended that only one automatic 30-month stay of approval per drug product per ANDA be allowed. *Id.* at ii.

61. See 21 U.S.C. § 355(j)(2), (j)(5), (b)(3), (c)(3) (2006); see also Barbara J. Williams, *A Prescription for Anxiety: An Analysis of Three Brand-Name Drug Companies and Delayed Generic Drug Market Entry*, 40 NEW ENGL. L. REV. 1 (2005) (analyzing the tactics of several brand-name companies to delay generic entry and suggesting further adjustments to Hatch-Waxman).

industry, particularly with respect to adequate compensation from the private sector to the government.⁶² Senator Ron Wyden requested that the General Accounting Office (GAO) investigate whether NIH had properly negotiated its CRADA with BMS, particularly with respect to revenues paid by BMS to NIH in exchange for data exclusivity.⁶³ Noting that BMS had worldwide sales of \$9,000,000,000 from 1993 until 2002 and that NIH only received \$35,000,000 in royalties during that period, the GAO report found that “NIH made substantial investments in research related to Taxol, but its financial benefits from the collaboration with BMS have not been great in comparison to BMS’s revenue from the drug.”⁶⁴ With respect to any government influence on the drug price charged by BMS, the report noted that the original CRADA referred to “NIH’s concern that Taxol be fairly priced given the public investment in Taxol, but it did not require that reasonable evidence be presented to show that this would occur.”⁶⁵ A “reasonable pricing” clause was incorporated into federal CRADA agreements until 1995, at which time it was dropped.⁶⁶

The development of Taxol illustrates an asymmetry between public investment and private benefit in some sectors of medical research, and the potential for government leverage over products in the pharmaceutical market by strategic transfer agreements that ensure public access to the products of federally-funded research.⁶⁷ However, government authorities

62. See GAO REPORT, *supra* note 20, at 1 (noting that “by 2001, [Taxol] had become the best selling drug in cancer history”).

63. *Id.* at 2.

64. *Id.* at 3.

65. *Id.* at 4 (noting that “[t]he federal government has been a major payer for Taxol, primarily through Medicare,” where such payments totaled nearly \$700 million over the five-year period prior to approval of the generic version of the drug). Senator Wyden stated that “NIH didn’t use its authority to require an accounting from the drug company that Taxol would be reasonably priced.” Senator Ron Wyden, Prepared Statement for Taxol News Conference, (June 6, 2003), http://wyden.senate.gov/media/speeches/2003/06062003_taxol_statement.html.

66. GAO REPORT, *supra* note 20, at 8. If an agency is not willing to monitor for reasonable pricing, a ready alternative is to design a royalty structure that more fairly recognizes the economic significance of the federally funded research and repays the taxpayers in aggregate. See Arti K. Rai, *The Information Revolution Reaches Pharmaceuticals: Balancing Innovation Incentives, Cost, and Access in the Post-Genomics Era*, 2001 U. ILL. L. REV. 173, 197-98 (2001) (noting the advantage of using a percentage of profits calculation to achieve a return to the government, and using that revenue for drug access, in contrast to a drug pricing regime). Much of the criticism of NIH might have been obviated had the agency initially negotiated for a more significant revenue return.

67. Scholars have noted the availability of government leverage and criticized the unwillingness of government agencies to assert their statutory authority in order to facilitate public access to federally funded research tools and pharmaceutical products. See Peter S. Arno and Michael H. Davis, *Why Don't We Enforce Existing Price Controls? The Unrecognized and Unenforced Reasonable Pricing Requirements Imposed Upon Patents Deriving in Whole or in Part from Federally Funded Research*, 75 TUL. L. REV. 631 (2001) (analyzing the march-in rights afforded to the federal government by the Bayh-Dole Act and their underuse); see also Arti K. Rai & Rebecca S. Eisenberg, *Bayh-Dole Reform and the*

must affirmatively decide to incorporate considerations of public benefit when they engage in negotiations to transfer federally-funded technologies. Alternatively, the government possesses the right to grant a compulsory license to a patent when circumstances would warrant, but it has generally declined to use this authority to facilitate access to medicines.⁶⁸ A lingering concern from the Taxol narrative, therefore, is the unresolved dilemma of fully leveraging the use of taxpayer-funded biomedical research to ensure access equity to the pharmaceutical products emerging from such research.

The Taxol history further illustrates the potential for unfair market dominance that can arise from manipulation of the regulatory processes that govern the patent interface between brand-name and generic drug manufacturers, and this phenomenon will be further discussed in Part III, *infra*, with respect to Tamoxifen. Recent reforms to the Hatch-Waxman process have eliminated some of the opportunities for brand-name pharmaceutical companies to block or delay generic competition.⁶⁹ However, patients may continue to access consumer relief in the form of private, state, or FTC antitrust enforcement actions when pharmaceutical market competition is delayed by illegal means, and this is where women's health advocates can maintain vigilance.

III. TAMOXIFEN

Breast cancer has a distinct relationship to the endocrine system—the group of hormones that are central to the maintenance of life. As the disease predominantly occurs in women, breast cancer cells have long been considered to be receptive to the presence or absence of female hormones, particularly estrogen.⁷⁰

Tamoxifen is a synthetic nonsteroidal compound that was developed in

Progress of Biomedicine, 66 LAW & CONTEMP. PROBS. 289, 310-11 (2003) (arguing for increased involvement by federal research granting agencies in order to ensure access to publicly funded research); Amy R. Schofield, *The Demise of Bayh-Dole Protections Against the Pharmaceutical Industry's Abuses of Government-Funded Inventions*, 32 J. L. MED. & ETHICS 777 (2004) (describing the unsuccessful march-in petition filed by patient advocates with NIH, seeking intervention with respect to the 400% increase in the price of the AIDS drug Norvir, manufactured by Abbott). *But see* NATIONAL INSTITUTES OF HEALTH, A PLAN TO ENSURE THAT TAXPAYER'S INTERESTS ARE PROTECTED 16 (2001) (asserting that a reasonable pricing clause in CRADA agreements was a disincentive to the private sector, that Bayh-Dole mediated technology transfer could not easily accommodate a revenue stream back to the government, and that the public benefits in the aggregate through the biomedical research facilitated by modern technology transfer policies).

68. See 28 U.S.C. § 1498 (2006) (giving the federal government the right to use and manufacture any patented invention, whether or not it is developed with federal funding, and to authorize third parties to do so as well, subject to the payment of compensation to the patent holder).

69. See THOMAS, *supra* note 16, at 23-25.

70. LOVE & LINDSEY, *supra* note 17, at 152.

the 1970s and shown to have antiestrogenic activity, meaning that it could bind to and block the cellular receptors for estrogen.⁷¹ Earlier clinical observations had shown that removal of the ovaries, where estrogen is produced, in women with breast cancer could cause remission of the cancer.⁷² These findings indicated that some breast cancer cells were dependent on estrogen for their maintenance, a fact that suggested a potential vulnerability of these cells. Later research established that some breast cancer cells have estrogen receptors (ER).⁷³ These are called ER-positive cells. Tumor cells from breast cancer patients are now routinely characterized for their ER status, and the presence of estrogen receptors on tumor cells creates therapeutic possibilities with more favorable prognostic implications.⁷⁴

Tamoxifen, therefore, as a compound with antiestrogenic activity, emerged as a promising hormonal treatment to block the estrogen stimulation of ER-positive tumor cells and decrease cell replication. Clinical studies that began in the 1970s revealed that Tamoxifen was effective in the treatment of advanced breast cancer, with reduced side effects in comparison to other hormonal alternatives.⁷⁵ Tamoxifen received FDA approval for the treatment of postmenopausal women with metastatic breast cancer in 1977.⁷⁶ As Tamoxifen came into widespread use, clinical observations suggested that the compound not only reduced existing tumors, but also reduced any recurrences of cancer in an unaffected breast; as a result, Tamoxifen was proposed as a chemopreventive agent for women at high risk of breast cancer. The Breast Cancer Prevention Trial administered Tamoxifen to healthy women over the age of sixty who were at high risk for breast cancer, and the results demonstrated a significant reduction in the expected number of cancers.⁷⁷ The study was controversial, however, as it required healthy women to take potentially dangerous hormonal supplements, and the National Women's Health Network (NWHN) led the opposition, with a particular focus on the possibility of Tamoxifen increasing the risk of uterine cancer.⁷⁸ In actual

71. MICHAEL W. DEGREGORIO & VALERIE J. WIEBE, TAMOXIFEN AND BREAST CANCER 29 (1999); *see also* LOVE & LINDSEY, *supra* note 17, at 194 (noting that Tamoxifen belongs to a class of drugs known as selective estrogen receptor modulators (SERM), which are compounds that have both estrogenic and anti-estrogenic effects).

72. DEGREGORIO & WIEBE, *supra* note 71.

73. *Id.* at 30.

74. LOVE & LINDSEY, *supra* note 17, at 276-77.

75. J. Ingle et al., *Randomized Clinical Trial of Diethylstilbestrol versus Tamoxifen in Postmenopausal Women with Advanced Breast Cancer*, 304 NEW ENGL. J. MED. 16 (1981).

76. DEGREGORIO & WIEBE, *supra* note 71, at 35.

77. *Id.* at 83.

78. BARRON H. LERNER, M.D., THE BREAST CANCER WARS 264 (2001).

fact, the clinical trial did reveal some increased risk of uterine cancer in patients, but supporters argued that the benefit from the reduction in breast cancer outweighed this risk.⁷⁹ In 1998, as a result of the chemoprevention trial, the FDA approved Tamoxifen as a preventive agent for women over age sixty at high risk for breast cancer.⁸⁰

Imperial Chemical Industries, PLC (ICI) obtained U.S. Patent 4,536,516 on the compound Tamoxifen in 1985. The drug was sold under the trade name, Nolvadex. The Hatch-Waxman Act had just been enacted in 1984, and the possibility of generic competition in this drug market was more likely as a result.⁸¹ Barr Laboratories, Inc., a generic drug manufacturer, filed an ANDA for approval of generic Tamoxifen with the FDA in December 1985, later amended in 1987 to contain a Paragraph IV certification that the ICI patent was invalid and unenforceable.⁸²

As allowed by Hatch-Waxman, ICI filed a patent infringement suit against Barr upon learning of Barr's intention to produce a generic Tamoxifen. The lawsuit resulted in a judgment that the ICI Tamoxifen patent was indeed invalid and unenforceable based on the fact that ICI withheld relevant information from the PTO when obtaining its patent.⁸³ ICI filed an appeal with the Federal Circuit.⁸⁴ In theory, a judgment that the Tamoxifen patent was invalid would remove any obstacle to a generic manufacturer wishing to enter this lucrative market. While the appeal was pending, however, ICI and Barr negotiated a settlement agreement in which Barr agreed to drop its challenge to the ICI patent.⁸⁵ The Federal Circuit agreed to vacate the invalidity judgment.⁸⁶ The settlement further provided that ICI would pay Barr \$21,000,000, supply Barr with ICI-manufactured Tamoxifen for sale, and that Barr would sell the drug under its own label at a price only 5 percent less than the brand-name drug price.⁸⁷ This generic drug price sharply departs from the expected price reductions that occur

79. *Id.* at 268.

80. DEGREGORIO & WIEBE, *supra* note 71, at 85.

81. *See supra* notes 41-48 and accompanying discussion.

82. *See Imperial Indus., PLC v. Barr Labs.*, 795 F. Supp. 619, 621 (S.D.N.Y. 1992).

83. *Id.*

84. *Imperial Chem. Indus., PLC, v. Heumann Pharma GMBH & Co.*, No. 92-1403, 1993 WL 118931, at *1 (Fed. Cir. Mar. 19, 1993). The Federal Circuit has been the exclusive federal appellate patent court since its creation in 1982.

85. *In re Tamoxifen Citrate Antitrust Litigation*, 277 F. Supp. 2d 121, 125 (E.D.N.Y. 2003).

86. *Imperial Chem.*, 1993 WL 118931 at *1 (granting joint motion to vacate judgment).

87. *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, 68 (2004) (discussing terms of the settlement agreement and noting that the five percent price difference sharply deviates from the traditional thirty to eighty percent price difference between generic and brand-name drugs).

when a generic enters the market and is an example of what has been called “pseudo-generics.”⁸⁸ This practice has been criticized as a collusive arrangement that facilitates joint market dominance by the brand-name company and its authorized generic licensee, depriving consumers of a truly competitive generic product.⁸⁹

Astra Zeneca (Zeneca) acquired ICI and its patents. Following the attempted generic entry by Barr, several other generic competitors attempted to enter the Tamoxifen market in the 1990s but were successfully sued by Zeneca for patent infringement of the same 1985 patent, in cases that were unaffected by the contrary finding of patent invalidity in the earlier Barr lawsuit.⁹⁰ As the first generic filer, Barr, despite the settlement with Zeneca, retained the option for the 180-day exclusivity entitlement allowed by Hatch-Waxman and could effectively stall any true generic competition.⁹¹

The settlement payment from a brand-name company to a generic competitor that terminates a patent infringement suit is often called a “reverse payment,” as the payment flows from plaintiff to defendant. Although settlements of patent disputes are generally favored, this particular practice has invited criticism that collusion between a dominant brand name and the rival generic allows both to control the market to the detriment of patient consumers and third-party payers.⁹² The practice also frustrates the role of patent litigation in eliminating weak patents that pose an unnecessary barrier to market competition. As a result, the practice has invited the scrutiny of the FTC because of the antitrust implications and potential for consumer harm.⁹³ Clearly, the absence of a competitive

88. See Jeremy Bulow, *The Gaming of Pharmaceutical Patents* 39, in 4 INNOVATION POLICY AND THE ECONOMY (Adam B. Jaffe et al. eds., 2004) (defining “pseudo-generics” as a “branded drug sold as a generic under license from the brand”). The phenomenon is also known by the term “authorized generics.”

89. See *id.* at 39-40.

90. See *Zeneca, Ltd. v. Novopharm Ltd.*, 111 F.3d 144 (Fed. Cir. 1997); *Zeneca Ltd. v. Pharmachemie, B.V.*, 37 F.Supp.2d 85 (D. Mass. 1999); *Zeneca Ltd. v. Mylan Labs*, 968 F.Supp. 268 (W.D. Pa. 1997), *rev'd*, 173 F.3d 829 (Fed. Cir. 1999).

91. See 21 U.S.C. § 355(j)(B)(iv) (2006). As one of the recent changes to the Hatch-Waxman Act, this 180-day period of exclusivity is now only available upon the first commercial marketing of the generic product and may be forfeited by patent settlement agreements between brand-name and generic competitors that raise antitrust issues. See THOMAS, *supra* note 16, at 24-25.

92. See Herbert Hovenkamp, Mark Janis, & Mark A. Lemley, *Anticompetitive Settlement of Intellectual Property Disputes*, 87 MINN. L. REV. 1719, 1759 (2003) (such settlements are presumptively anti-competitive, absent certain showings by the infringement plaintiff). The reverse payments are also called “exclusion payments.” *Id.* at 1749.

93. See FTC Report, *supra* note 56, at 25-37. Certain settlement agreements between brand-name and generic pharmaceutical competitors are now required to be filed with the Federal Trade Commission and the Department of Justice. See THOMAS, *supra* note 16, at 571-72.

generic marketplace will keep drug prices high.

In 2001, a coalition of consumer groups filed class action lawsuits against Zeneca and Barr, alleging that the 1993 reverse payment settlement violated Section 1 of the Sherman Act.⁹⁴ The plaintiffs alleged that the settlement allowed Zeneca and Barr to resuscitate a patent declared invalid, control the entire U.S. Tamoxifen market, and exclude competition from other generic manufacturers, effectively keeping drug prices high and reducing patient access.⁹⁵ The district court dismissed the complaint, finding that the plaintiffs suffered no antitrust injury, noting that none of the other generic competitors that might have entered the market had succeeded in invalidating the Zeneca patent, an outcome that was not the result of the settlement at issue.⁹⁶ The verdict was affirmed by the Second Circuit, which declared that reverse payment settlements were not per se unlawful provided that the underlying litigation was not a sham and that the settlement did not constitute an unlawful extension of a valid patent monopoly.⁹⁷ The Tamoxifen decision from the Second Circuit is in direct contrast with the Sixth Circuit adoption of a per se illegality standard for such settlements.⁹⁸ In an enforcement action by the FTC against Schering-Plough, the Eleventh Circuit did not adopt a per se illegality rule but endorsed an inquiry into the validity of the underlying patent.⁹⁹ Although the Supreme Court did not grant certiorari in *Schering-Plough*, there is now significant disagreement among the appellate circuits regarding the standard for reviewing these settlements, and the Tamoxifen case presents an attractive opportunity for the Court to clarify the patent/antitrust interface with respect to reverse payments in pharmaceutical patent settlements.¹⁰⁰ The phenomenon of a reverse payment that followed a judgment of the invalidity of the Tamoxifen patent is particularly egregious

94. See Sherman Act, 15 U.S.C. § 1 (2006) (declaring any contract in restraint of trade or commerce among the states to be illegal).

95. *Tamoxifen Antitrust Litigation*, 277 F.Supp.2d at 123 (noting that plaintiffs included senior citizen groups, labor unions, and health care advocates); see also Press Release, Prescription Access Group, Consumer Groups Charge Price Collusion on Key Breast Cancer Drug (May 9, 2003), http://www.prescriptionaccess.org/index.php?doc_id=574 (quoting Kim Shellenberger, director of the Prescription Access Litigation Project: "These companies have colluded to keep a life-saving drug priced beyond the reach of many breast cancer patients").

96. *Tamoxifen Antitrust Litigation*, 277 F.Supp.2d at 136.

97. *In re Tamoxifen Citrate Antitrust Litigation*, 429 F.3d 370, 2005 U.S. App. LEXIS 23653 (2d Cir. 2005), *amended and superseded by* 466 F.3d 187, 2006 U.S. App. LEXIS 22154 (2d Cir. N.Y. 2006). A petition for rehearing was denied in September 2006.

98. See *In re Cardizem*, 332 F.3d 896 (6th Cir. 2003).

99. See *Schering-Plough v. FTC*, 402 F.3d 1056 (11th Cir. 2005), *cert. denied*, 126 S. Ct. 2929; 165 L. Ed. 2d 977; 2006 U.S. LEXIS 5128 (June 26, 2006).

100. Petition for Writ of Certiorari, *Tamoxifen Antitrust Litigation*, 429 F.3d 370 (No. 06-830), available at http://www.orangebookblog.com/Tamoxifen_20Cert_20Petition.pdf. The petition for Supreme Court review was filed on Dec. 13, 2006.

and warrants heightened scrutiny from the judiciary.

The lucrative Tamoxifen market generated significant maneuvering of the available patent strategies for the market leader to maintain a dominant position using Hatch-Waxman procedures, as was also observed with respect to Taxol, *supra* Part II. The strategies succeeded in delaying generic competition until the expiration of the Zeneca patent in 2002.¹⁰¹ It is important to note that nearly a decade passed between the original judgment that the Zeneca Tamoxifen patent was invalid and the introduction of generic alternatives.

The Tamoxifen history and the methods by which Zeneca maintained its market dominance have raised the visibility of two phenomena in the pharmaceutical sector: pseudo-generics and reverse payments in patent settlements. Legislation has been introduced to reduce the introduction of pseudo-generics¹⁰² and to more effectively monitor anticompetitive settlement agreements.¹⁰³ It is possible that health consumers may continue to encounter unfair competition in the pharmaceutical marketplace when companies unfairly collude, and the breast cancer marketplace could continue to be an attractive target for anticompetitive conduct. Patient advocates, however, have also entered the debate with a vigorous litigation strategy that reflects a sophisticated understanding of the patent/antitrust interface. The FTC has increased its surveillance of patent settlements that disadvantage patients and insurers.¹⁰⁴ This vigilance by citizens and regulatory authorities could reduce future opportunities for anticompetitive behavior in the pharmaceutical sector.

IV. HERCEPTIN

The modern approach to cancer research is to comprehend the cancer cell through a precise analysis of its molecular features, particularly its genes and proteins. Cancer cells have unique surface features. When certain molecules appear predominantly on cancer cells and not on normal cells, they are assumed to have some importance in the growth of the cancer cells and are often referred to as markers or antigens.¹⁰⁵

101. See FOOD & DRUG ADMIN., ELECTRONIC ORANGE BOOK (2006), <http://www.fda.gov/cder/ob/default.htm> (noting that generic competition in the Tamoxifen market is provided by Aegis, Andrx, Barr, Ivax, Mylan, Pharmachemie, Roxane, and Teva).

102. See S. 3695, 109th Congress (2006) (banning the sale of authorized generic drugs during the first ANDA filer's 180 day exclusivity period).

103. See Preserve Access to Affordable Generics Act, S. 3582, 109th Congress (2006) (prohibiting brand-name drug companies from entering into "reverse payment" settlements with generic drug companies).

104. See THOMAS, *supra* note 16, at 571-72 (noting that such settlements are now required to be filed with the Federal Trade Commission and the Department of Justice).

105. ALBERTS ET AL., *supra* note 4, at 1358.

Characterization of isolated breast cancer cells has revealed a number of unique biochemical traits. In particular, about twenty to thirty-five percent of breast cancer cells show a distinct overabundance of a specific protein on their surface, known as Her-2.¹⁰⁶ Dennis Slamon and coworkers discovered that breast cancer cells with an overexpression of Her-2 signaled a particularly aggressive form of breast cancer.¹⁰⁷ In the late 1980s, these kinds of observations gave rise to the field of molecular oncology, which is the application of molecular biology to cancer. The early biotechnology companies were introducing novel therapeutic compounds, such as recombinant proteins, which are produced by cellular processes, rather than chemical synthesis.¹⁰⁸ A promising response to the observation of novel proteins on the surface of the cancer cell is to neutralize them with an antibody, a specific protein that will recognize and bind to the surface molecule. Because of its specificity, a monoclonal antibody is the preferred therapeutic form for patient administration.¹⁰⁹ Such antibodies are classified by the FDA as biologics.¹¹⁰ The FDA regulates biologics (blood products, vaccines, proteins, antibodies, gene therapy products) separately from other pharmaceuticals.¹¹¹ These products present novel challenges for regulation and approval. For monoclonal antibodies to be approved as therapeutics, issues of product consistency and manufacturing reliability have particular force.

106. S.A. Aronson, *Amplification of a Novel v-erb-B-related Gene in a Human Mammary Carcinoma*, 229 *SCIENCE* 974 (1985). The gene is formally known as Her-2/neu, acknowledging the research origins of the discovery and the molecular relationship of the gene to the human epidermal growth factor receptor family. See BAZELL, *supra* note 18, at 33-34.

107. D.J. Slamon et al., *Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the Her-2/neu Oncogene*, 235 *SCIENCE* 177 (1987). Because the overexpressed surface protein is involved in a biochemical pathway that stimulates cell reproduction, an antibody to the protein can have an anticancer effect due to its interruption of this signaling mechanism, thus inhibiting cell replication. See BAZELL, *supra* note 18, at 42.

108. See GARY ZWEIGER, *TRANSDUCING THE GENOME: INFORMATION, ANARCHY, AND REVOLUTION IN THE BIOMEDICAL SCIENCES* 161 (2001). The early biotechnology companies began to form in the 1970s; Genentech was formed in 1976. *Id.*

109. See Georges Kohler & Cesar Milstein, *Continuous Cultures of Fused Cells Secreting Antibody of Predefined Specificity*, 256 *NATURE* 495 (1975) (describing the technique for producing monoclonal antibodies by a cell culture technique that assures continuous clonal replication, guaranteeing product purity). This technique revolutionized immunology, making it possible to obtain significant quantities of a purified antibody.

110. The terms “biopharmaceutical” or “biotechnology medicines” are also used to describe therapeutic compounds produced by cellular processes, rather than industrial laboratory manufacture. See GARY WALSH, *BIOPHARMACEUTICALS: BIOCHEMISTRY AND BIOTECHNOLOGY* 2 (2003).

111. A manufacturer seeking approval of a biologic submits a Biologics License Application (BLA) to the FDA. See *id.* at 80. Within the FDA, monoclonal antibody applications are reviewed by the Center for Drug Evaluation and Research (CDER). See FDA, *Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research*, <http://www.fda.gov/oc/combinatoin/transfer.html> (last visited Dec. 29, 2006).

Genentech, a biotechnology company, recognized that the molecular approach to cancer treatment was likely to yield promising therapeutic compounds, but it was cautious with respect to the resources it devoted to the nascent field.¹¹² In response to the vigorous advocacy of breast cancer patient advocates, however, Genentech sponsored clinical trials involving the administration of a Her-2 antibody, known as trastuzumab, to patients with advanced breast cancer. It was given the trade name Herceptin.¹¹³ Following the demonstration that the antibody reduced or eliminated tumors in a significant number of patients, Genentech filed a Biologics License Application (BLA) with the FDA in 1998 and was granted approval for the use of Herceptin to treat patients with metastatic breast cancer whose tumors overexpress the Her-2 protein.¹¹⁴ Herceptin has been used in treatment since 1998 and has been described as the first clinically approved drug to target a specific molecular target.¹¹⁵ It is an early illustration of pharmacogenomics, the clinical convergence of genetics and pharmacology, which attempts to identify the patients that will benefit from certain therapeutics based on their genetic status.¹¹⁶ More recently, clinical trials of Herceptin in combination with Taxol for the treatment of early-stage breast cancer have shown very promising results, and Genentech has received FDA approval for this use of Herceptin.¹¹⁷

Genentech has obtained several patents that cover the antibodies and methods for their production.¹¹⁸ The prominence of Herceptin in the treatment of breast cancer has increased rapidly, with an accompanying financial gain for Genentech.¹¹⁹ Chiron Corporation, another of the early

112. See BAZELL, *supra* note 18, at 45-47.

113. For a detailed treatment of the clinical development of the Her-2 monoclonal antibody and the role of Genentech and breast cancer activists, *see id.* at 109-177.

114. See FOOD & DRUG ADMIN., CENTER FOR DRUG EVALUATION & RESEARCH, PRODUCT APPROVAL INFORMATION—LICENSING ACTION (1998), www.fda.gov/cder/foi/appletter/1998/trasgen092598L.htm.

115. See Nickolas Papadopoulos et al., *The Role of Companion Diagnostics in the Development and Use of Mutation-Targeted Therapies*, 24 NATURE BIOTECHNOLOGY 985, 989 (2006).

116. See Kathryn A. Phillips, *The Intersection Of Biotechnology And Pharmacogenomics: Health Policy Implications*, 25 HEALTH AFFAIRS, 1271, 1274 (2006).

117. See Edward H. Romond et al., *Trastuzumab Plus Adjuvant Chemotherapy for Operable Her-2-Positive Breast Cancer*, 353 NEW ENGLAND JOURNAL OF MEDICINE 1673 (2005). The FDA approval was granted in November 2006. Press Release, F.D.A. Expands Use of Herceptin for Early Stage Breast Cancer After Primary Therapy (Dec. 12, 2006), <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01511.html>.

118. Monoclonal Antibodies Directed to the Her-2 Receptor is a foundational patent to the compound. U.S. Patent No. 5,677,171 (filed Aug. 5, 1994) (issued Oct. 14, 1997).

119. See Press Release, Genentech Biooncology, Genentech Announces Full Year and Fourth Quarter 2005 Results (Jan. 10, 2006), <http://www.gene.com/gene/news/pressreleases/display.do?method=detail&id=9287> (stating that United States sales of Herceptin (Trastuzumab) increased fifty-six percent from \$479.0 million in 2004 to \$747.2 million in 2005); *see also* Jennifer Barrett, *No Longer a Death Sentence*,

biotechnology companies, sued Genentech for patent infringement soon after the product launch, alleging that its production of Herceptin infringed the Chiron patent on Her-2 monoclonal antibodies.¹²⁰ Chiron claimed that the effective filing date of its own patent was 1984.¹²¹ The disadvantage of an early filing date in a rapidly developing scientific field is that a patent application may not have fully described the subsequent developments in the field. Genentech alleged that the Chiron patent was invalid in that it did not fully describe nor enable the production of the actual Herceptin antibody because Herceptin is a chimeric (humanized) human/mouse antibody engineered to minimize immune reactions in a patient, a design that the Chiron patent claims did not cover.¹²² Formally, these statutory defects are described in U.S. patent law as a lack of written description and enablement.¹²³ A jury determined that Chiron's earliest filings did not enable or describe patent claims that covered the humanized antibody, meaning that the patent did not cover the Genentech product, and this decision was affirmed by the Federal Circuit.¹²⁴ Genentech, therefore, survived this patent challenge to Herceptin.

There are patent-related issues that are surfacing as biotechnology matures and as patients bring the same expectations of a competitive pharmaceutical marketplace to the biotechnology medicines that they encounter. The pricing of Herceptin has reflected the generally high prices of new therapeutics developed from biotechnology and is currently priced at approximately \$48,000 per patient per year.¹²⁵ This cost that has been criticized by patient advocates and will likely impact its availability for the treatment of early stage breast cancer, although major insurance companies provide coverage for its use in the treatment of metastatic breast cancer.¹²⁶ The market reality of a targeted therapy such as Herceptin is that the

NEWSWEEK, Oct. 25, 2005, at 2-3 (describing Herceptin as possibly the most important new breast cancer treatment of the last few years).

120. Antigen-binding Sites of Antibody Molecules Specific for Cancer Antigens, U.S. Patent No. 6,054,561 (filed June 7, 1995) (issued Apr. 25, 2000).

121. The significance of an earliest effective filing date of a patent is that only prior art existing before that date can be used to defeat the patentability of the invention.

122. *Chiron v. Genentech*, 363 F.3d 1247, 1256 (Fed. Cir. 2004).

123. See 35 U.S.C. § 112, first paragraph.

124. *Chiron*, 363 F.3d at 1247.

125. See BREAST CANCER ACTION NEWSLETTER #89, *Herceptin Reports Reveal a Mixed Bag*, (Breast Cancer Action) January 2006, <http://www.bcaction.org/Pages/SearchablePages/2005Newsletters/Newsletter089H.html> ("The annual cost of Herceptin, manufactured by Genentech, is a whopping \$48,000. BCA and other public health advocates have expressed concerns over who will have access to this drug and what impact the skyrocketing prices of biotech therapies will have on an already-troubled health care system.").

126. See Phillips, *supra* note 116, at 1275 (noting the availability of insurance coverage for patients with metastatic cancer).

scientific precision of the therapeutic compound can also narrow the target population for the treatment, a factor that can increase price.

The demand for Herceptin and its relatively high price is a paradigmatic illustration of the dilemma that accompanies the introduction of biotechnology-derived pharmaceuticals into the health care system. The Hatch-Waxman statutory framework which facilitates the development of generic alternatives to brand-name conventional pharmaceuticals has been discussed previously with respect to Taxol (Part II, *supra*) and Tamoxifen (Part III, *supra*). To date, however, the FDA has not provided an analogous generic approval pathway for biologics,¹²⁷ although it has considered how two monoclonal antibodies from separate manufacturers would be evaluated for similar clinical effect.¹²⁸ Of course, a generic manufacturer can file a completely new BLA for the approval of a generic biologic upon the expiration of a patent related to the brand-name product. However, significant time for regulatory approval may elapse such that de facto market exclusivity remains for the brand-name company, forestalling the reduction in product cost that would be expected. The premise of Hatch-Waxman expedited generic entry is that the latter market entrant can rely on the clinical data submitted by the first entrant, if the products are bioequivalent.¹²⁹ The guarantee that a generic biologic will be bioequivalent or identical to an approved brand-name product is less assured for products produced by cellular processes, which are biologically dynamic and may also rely on the use of proprietary materials. There is no resolution yet, but the FDA has continued to gather input as it considers how to facilitate the development of a meaningful generic market for biotechnology medicines.¹³⁰ Legal challenges have been filed, however, that allege undue delay on the part of the FDA in formulating a generic approval process.¹³¹ In addition, legislation has been introduced which

127. See David M. Dudzinski, *Reflections on Historical, Scientific and Legal issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies*, 60 FOOD DRUG L. J. 143-44 (2005). Generic biologics are also called biogenerics or follow-on biologics.

128. See *id.* at 228-29.

129. See THOMAS, *supra* note 16, at 14. Antibodies are proteins, composed of amino acids, so determinations of bioequivalence or biosimilarity will involve a consideration of the degree of amino acid differences that can be tolerated between two compared proteins in order to maintain clinical equivalence.

130. See FDA, Public Workshop: Scientific Considerations Related to Developing Follow-On Protein Products, September 14-15, 2004, <http://www.fda.gov/cder/meeting/followOn/followOnPresentations.htm>.

131. See The States of Kansas, Minnesota, Vermont, and Wisconsin, Citizen Petition, 2006P-0306 (Aug. 3, 2006), available at <http://www.fda.gov/ohrms/dockets/dockets/06p0306/06p-0306-cp00001-vol1.pdf>. Sandoz challenged an undue delay by the FDA in granting approval of its ANDA application to market Omnitrope, which is recombinant human growth hormone. *Sandoz, Inc. v. Leavitt*, 427 F. Supp. 2d 29 (D.D.C. 2006).

would set up a generic approval pathway for biologics.¹³² The visibility of Herceptin, among other products, will certainly increase pressure on regulatory authorities to expedite the development of generic alternatives, and the breast cancer patient advocacy groups will likely play a significant role at this juncture as they did in the early development of Herceptin.¹³³ The regulatory processes that emerge should ideally make it possible for the generic product to appear before or at the expiration of patents relating to the brand-name product, so that monopoly pricing does not unduly persist. In that way, an original patent can act as a legitimate incentive for innovation but not as a superfluous obstacle to market competition. When a generic approval process is finally implemented, the patent conflicts over Taxol and Tamoxifen, for example, should alert cancer patient advocates to the vigilance required to ensure that a generic market for biologics is as fully developed as the law contemplates.

Access issues that ensue from the high prices for biologics, such as Herceptin, are likely to increase as cancer research assumes a distinct molecular pedigree, resulting in the development of therapies that offer clinical advantages due to precise targeting. Acute questions regarding access arise where a specific patient population is identified as the optimal beneficiaries of a particular therapy through pharmacogenomics. Herceptin is a prominent example of this approach, where the patients with Her-2 positive tumors are those who can likely benefit from access to Herceptin. The advent of pharmacogenetic considerations in cancer treatment will increase pressure to make these biologics widely available, in order that the therapeutic precision afforded by molecular oncology is fully exploited.

V. BRCA1 AND BRCA2 GENES

The molecular approach to cancer research resonates with a long-standing desire to identify any genetic predisposition to cancer. Identifying any genetic basis of cancer presents the possibility of revealing risk in affected populations and taking measures to reduce that risk. Many cancer-related genes have been identified, so-called oncogenes, which can transform a normal cell to a cancerous one, and so-called tumor suppressor genes, which fail to block tumor development when mutations occur in these genes.¹³⁴

The work of geneticist Mary-Claire King and colleagues led to the identification of a group of families that exhibit a high number of early-

132. See Access to Life-Saving Medicines Act, H.R. 6257, 109th Congress (2006) (establishing an approval process for the FDA review of “comparable biological products”).

133. See BAZELL, *supra* note 18, at 115-132.

134. ALBERTS ET AL., *supra* note 4, at 1333.

onset cases of breast and ovarian cancer. In 1997, King announced that these families were being studied for an apparent genetic vulnerability to these diseases, and that a possible gene of interest had been mapped to chromosome 17.¹³⁵ This announcement prompted an intense competition among research groups to locate the specific gene that was responsible for this early-onset form of these cancers. The first group to characterize the full-length gene sequence was led by Mark Skolnick and colleagues at the University of Utah who identified the specific gene on chromosome 17, named BRCA1.¹³⁶ The Skolnick group subsequently applied for a patent on this DNA sequence and was awarded U.S. Patent No. 5,693,473 on December 2, 1997.¹³⁷ This patent was licensed to the Utah-based Myriad Genetics, Inc. The work of King's group at the University of California was patented and licensed to OncorMed, Inc.¹³⁸ Patent infringement litigation subsequently ensued between Myriad and OncorMed, with Myriad finally prevailing and purchasing the OncorMed patents, with the result that Myriad gained the dominant U.S. patent position with respect to the BRCA1 gene.¹³⁹

Further research on breast cancer genetics subsequently identified a second gene implicated in the heightened risk of breast and ovarian cancer observed in families that carried mutations in the gene. It was identified as BRCA2 and localized to chromosome 13; Myriad obtained patents to this gene sequence as well.¹⁴⁰

Soon after BRCA1 and BRCA2 were identified, in 1996, Myriad introduced BRCAAnalysis®, the first commercial genetic test to detect mutations in the breast cancer genes. By 1999, Myriad was able to offer a test that provided a full-length DNA sequence analysis.¹⁴¹ A number of other American laboratories offered a breast cancer genetic test as part of clinical research programs, with investigators offering different technical testing methods, but these efforts were challenged by Myriad as the holder

135. Jeff M. Hall et al., *Linkage of Early-Onset Familial Breast Cancer to Chromosome 17q21*, 250 *SCIENCE* 1684 (1990).

136. Yoshio Miki et al., *A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene*, 266 *SCIENCE* 66 (1994).

137. *Linked Breast and Ovarian Cancer Susceptibility Gene*, U.S. Patent No. 5,693,473 (filed June 7, 1995) (issued Dec. 2, 1997).

138. *Genetic Markers for Breast, Ovarian, and Prostatic Cancer*, U.S. Patent No. 5,622,829 (filed Apr. 19, 1995) (issued Apr. 22, 1997).

139. Bryn Williams-Jones, *History of A Gene Patent: Tracing the Development and Application of Commercial BRCA Testing*, 10 *HEALTH L. J.* 123, 132-133 (2002). Myriad holds at least eight U.S. patents to date related to the BRCA1 and BRCA2 genes; issued as recently as U.S. Patent No. 5,837,492, *Chromosome 13-Linked Breast Cancer Susceptibility Gene*, on November 17, 1998.

140. Richard Wooster et al., *Identification of the Breast Cancer Susceptibility Gene BRCA2*, 378 *NATURE* 789 (1995).

141. Williams-Jones, *supra* note 139, at 134.

of the patents to the actual gene sequences.¹⁴² Myriad's enforcement of its patent rights require any licensees to submit clinical samples directly to the Myriad laboratory for testing, a result that has been criticized on scientific grounds because it unduly limits the development of multiple technical approaches to genetic testing.¹⁴³ A recent study by Mary-Claire King and colleagues reported that twelve percent of the women who had received a negative test result from commercial BRCA1 and BRCA2 testing in fact possessed undetected cancer-predisposing mutations in at least one of these genes.¹⁴⁴ The implication of this work is that a scientific monopoly facilitated by patent rights undermines the development of multiple technical approaches, which collectively offer the most thorough testing climate.¹⁴⁵ This outcome can partly be traced to the existence of patent rights, but it more precisely reflects choices by the patent holder in the exercise of its rights. It is possible to imagine an alternative scenario, where a patent on a DNA sequence is widely licensed for a reasonable fee and with minimal restrictions.

Despite the dominance of Myriad over breast cancer testing in the United States, private insurance will often pay for the test for individuals meeting certain criteria.¹⁴⁶ The cost will vary, as the first individual in a family to

142. *Id.* at 136. For example, researchers at the University of Pennsylvania who offered BRCA testing received cease and desist letters from Myriad, threatening litigation unless they took a license to the Myriad patents. *Id.* Myriad granted the NIH and the NCI at-cost licenses (approximately \$1200 per test). *Id.*

143. *See id.* at 139 (noting technical limits to Myriad testing methods identified by researchers at the Institut Curie).

144. *See* Tom Walsh et al., *Spectrum of Mutation in BRCA1 BRCA2, CHEK2, and TP53 in Families at High Risk of Breast Cancer*, 295 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 1379, 1386 (2006) ("Clinical testing options for BRCA1 and BRCA2 are limited in the United States. In contrast to genetic testing for BRCA1 and BRCA2, genetic testing for other cancer susceptibility genes (MSH2, MLH1, PTEM, TP53, etc.) are available from numerous profit and not-for profit laboratories with a range of testing options and prices.").

145. *See* Vural Odzemir et al., *Shifting Emphasis from Pharmacogenomics to Theragnostics*, 24 NATURE BIOTECHNOLOGY 942, 943 (2006) ("[T]he BRCA patents give Myriad the ability to constrain research-oriented applications of BRCA patents and particularly head-to-head comparisons of which genotyping methodology or test product is most informative for clinical management of the susceptibility to breast cancer."). A contrasting climate exists for Her-2 testing, where Genentech has facilitated a robust set of testing options, due to the fact that its Herceptin product is targeted to women with specific types of cancers and obstacles to testing would reduce demand for the drug. *See* John H. Barton, *Emerging Issues in Patent Diagnostics*, 24 NATURE BIOTECHNOLOGY 939, 940 (2006).

146. Information regarding access to the genetic tests is maintained by FORCE (Facing Our Risk of Cancer Empowered), an advocacy group for women with genetic susceptibility to breast cancer. *See* FORCE: Facing Our Risk of Cancer Empowered, http://www.facingourrisk.org/finding_health_care/financial_help.html?PHPSESSID=62e28f3a30cafa005a5d6fc3ba29057a (last visited Nov. 30, 2006) (stating that "most insurance companies will cover the cost of genetic testing in individuals who either have a personal history or family history of cancer and who meet certain guidelines" and that similar criteria apply to Medicare recipients). *See generally* Am. Soc'y of Clinical Oncology, *American*

get genetic testing will likely undergo full-length sequencing of the BRCA1 and BRCA2 genes, but subsequent family members could undergo more limited testing to determine whether they carry particular mutations identified in the primary case.¹⁴⁷

Patent rights are national in origin, and Myriad encountered a different patent climate outside the U.S. Myriad obtained BRCA1 and BRCA2 patents in Canada, New Zealand, and the European Patent Office (EPO).¹⁴⁸ There has been significant resistance to these patents in Europe, with serious consequences for Myriad due to the fact that an opposition can be filed against an EPO patent, an option not afforded to challengers of U.S. patents.¹⁴⁹ Oppositions have been filed against several of the Myriad EPO patents, with the French research organization Institut Curie taking the initiative.¹⁵⁰ Myriad's patent position was severely weakened when the EPO revoked EP 699 754 and maintained EP 705 902 and EP 705 903 in amended form, all of which pertain to BRCA1.¹⁵¹ More recently, Myriad

Society of Clinical Oncology Policy Statement Update: Genetic Testing for Cancer Susceptibility, J. CLINICAL ONCOLOGY June 15, 2003, at 7 (noting that Medicaid determines coverage for genetic testing on a state by state basis, but that no information is available on which states do and which states do not provide such coverage); LOVE & LINDSEY, *supra* note 17, at 179 (estimating the cost for a BRCA test to cost approximately \$3,000 for full DNA sequence testing and \$400 for specific mutation testing).

147. See Nancie Petrucelli et al., *BRCA1 and BRCA2 Hereditary Breast/Ovarian Cancer*, GENEREVIEWS, Sept. 4, 1998, at 5-6, available at <http://www.geneclinics.org/servlet/access?id=8888891&key=vEb6tt6TXdJAY&fcn=y&fw=bJu4&filename=/reviewsearchdz.html>.

148. See Jordan Paradise, *European Opposition to Exclusive Control Over Predictive Breast Cancer Testing and the Inherent Implications for U.S. Patent Law and Public Policy: A Case Study of the Myriad Genetics BRCA Patent Controversy*, 59 FOOD DRUG L.J. 133 (2004). In the European Patent Office, Myriad was granted EP 699 754, EP 705 902, and EP 705 903 (related to BRCA1) and EP 785 216, EP 858 467, and EP 1260 520 (related to BRCA2).

149. See European Patent Convention art. 99, Oct. 5, 1973 (declaring that the grounds for an opposition must be drawn from Articles 52 to 57 of the Convention). U.S. patent law does not allow for an opposition to be filed by an unrelated third party; patent invalidity determinations generally occur during infringement litigation between a patent owner and an accused infringer. However, there are proposals for change. See H.R. 2795, Patent Reform Act of 2005, § 324 ("The issues of invalidity that may be considered during the opposition proceeding are double patenting and any of the requirements for patentability set forth in sections 101, 102, 103, 112 and 251(d).").

150. See Michael Balter, *Transatlantic War Over BRCA1 Patent*, 292 SCIENCE 1818 (2001) (noting that the Institut Curie filed an opposition to the first Myriad patent (EP 699 754) after its own research revealed the existence of a mutation in the BRCA1 gene that was not detected by Myriad's own testing).

151. EP 699 754 was revoked by the EPO in May, 2004, for a lack of inventive step (EPC Article 56). See Press Release, European Patent Office, "Myriad/ Breast Cancer" Gene Patent Revoked After Public Hearing (May 18, 2004), http://www.european-patent-office.org/news/pressrel/2004_05_18_e.htm. Subsequently, the other BRCA1 patents have been amended by the EPO (narrowed scope) following separate opposition challenges led by the Institut Curie. See Press Release, Institut Curie, Another Victory for Opponents of Patents Held by Myriad Genetics: European Patent Office Rejects the Essential Points of BRCA1 Gene Patents (Jan. 31, 2005), <http://www.curie.fr/upload/presse/myriadpatents310105.pdf>.

has sustained an adverse result in an opposition filed by the Institut Curie against its EP 785 216 (BRCA2).¹⁵² Myriad's patent position in Europe has been severely weakened by the series of oppositions, and it does not dominate breast cancer genetic testing as it does in the United States. The European Parliament passed a resolution that opposed the issuance of such patents by the EPO.¹⁵³

Patents on the breast cancer genes implicate the larger issue of the patenting of DNA, which has been a controversial issue for years. A recent report states that nearly twenty percent of all protein-coding human genes have been patented, with the majority patented by private biotechnology companies.¹⁵⁴ Several lines of conflict result from this patenting. One is whether such patents should be granted at all.¹⁵⁵ Many commentators have discussed the difficulties that DNA patents may pose for biomedical research.¹⁵⁶ A second question is whether mechanisms should be established to ensure access to patented DNA sequences, which cannot be invented around.¹⁵⁷ A recent study concludes that patents on genes used in

152. The EPO press release stated: "The patent claim now relates to the use of a particular nucleic acid carrying a mutation of the BRCA 2-gene which is associated with a predisposition to breast cancer for in vitro-diagnosing of such a predisposition in Ashkenazi-Jewish women." See Press Release, European Patent Office, Patent on "Breast Cancer Gene 2" Patent Maintained in Amended Form after Public Hearing (June 29, 2005), http://www.european-patentoffice.org/news/pressrel/2005_06_29_e.htm; see also Karen Iris Tucker, *Breast Cancer Gene Patent Causing a Furor*, THE FORWARD, Aug. 5, 2005 (noting the European Society of Human Genetics' criticism of the patent that "[t]his is the first time that a racial or ethnic group has been specifically singled out as a diagnostic target in a gene patent claim").

153. See Resolution on the Patenting of BRCA1 and BRCA2 ("breast cancer") Genes, EUR. PARL. DOC. (2001), available at <http://www.cptech.org/ip/health/biotech/eu-brca.html> (noting that a monopoly on breast cancer genetic testing "could seriously impede or even completely prevent the further use of existing cheaper and more effective tests for the breast cancer genes BRCA1 and BRCA2").

154. Kyle Jensen & Fiona Murray, *Intellectual Property Landscape of the Human Genome*, 310 SCIENCE 239 (2005). (referencing a study of 4,382 of the 23,688 genes in the National Center for Biotechnology Information's database that showed that sixty-three percent of the patents are assigned to private firms and that, of the top ten gene patent assignees, nine were based in the United States).

155. See E-mail from Fran Visco, President, National Breast Cancer Coalition, to Mark Nagumo, Commissioner of Patents and Trademarks, U.S. Patent and Trademark Office (Mar. 22, 2004), <http://www.uspto.gov/web/offices/com/sol/comments/utilguide/nbcc.pdf> (stating that the practice of gene patenting is against the public interest and harmful to research, in response to the PTO's invitation for public comments on its decision of whether to raise its standards for utility and written description, a decision with particular effects on gene patents).

156. See generally Rebecca S. Eisenberg, *Genetics and the Law: Patenting the Human Genome*, 39 EMORY L.J. 721 (1990); Rebecca S. Eisenberg, *Re-Examining the Role of Patents in Appropriating the Values of DNA Sequences*, 49 EMORY L.J. 783 (2000); Arti K. Rai, *Intellectual Property Rights In New Technology*, 34 WAKE FOREST L. REV. 827 (1999); Lori Andrews, *The Gene Patent Dilemma: Balancing Commercial Incentives with Health Needs*, 2002 HOUS. J. L. & POL'Y 65 (2002); Eileen M. Kane, *Splitting the Gene: DNA Patents and the Genetic Code*, 71 TENN. L. REV. 707 (2004).

157. Legislation was introduced (but not enacted) in the 107th Congress (H.R. 3967) that

diagnostic testing have posed the most serious obstacle for researchers, but notes that the acutely restrictive climate created by the Myriad BRCA1 and BRCA2 patents is a “cautionary tale” for other gene patent holders, who are disinclined to enforce their patents in a manner that disadvantages intellectual development of the research field.¹⁵⁸

Both researchers and patients have been affected by the management of the Myriad patents. The monopoly position held by Myriad has consequences for patient access and expense, and for research quality, which is optimized when multiple investigators address the same research problem. The continued dominance of the BRCA1 and BRCA2 patents, especially in the United States, may have consequences for the role of genetic testing in reducing the incidence of breast cancer and for the confidence of patients in their results from existing commercial tests. The ongoing scrutiny of DNA patenting by patient advocates and the scientific community is certain to continue, and patent strategies that could inhibit scientific progress or undermine patient confidence are likely to encounter resistance.

CONCLUSION

Effective health care for women relies on a nexus of scientific, medical, and legal regimes. This Article has examined an intersection of patent law with women’s health issues in order to characterize the interface between patent incentives and patent barriers. The analysis of patent conflicts that have accompanied the development and dissemination of treatments and diagnostic methods for breast cancer clearly illustrates the nexus between intellectual property law and the achievement of an effective health regime for women. Diverse legal scenarios reveal how the procurement and stewardship of patents that control the use of important therapeutic and diagnostic compounds impact the development of a competitive pharmaceutical market and resulting patient access. The patent disputes range from those that arise in a mature pharmaceutical market to those that can only arise from new developments in biotechnology. An understanding of patent issues is central to the efforts to improve health care for women in order to identify points of leverage where advocacy can be effective. As

would have created a research exemption from infringement for research on genetic sequence information and an infringement exemption for genetic diagnostic testing. See also NATIONAL INSTITUTES OF HEALTH, BEST PRACTICES FOR THE LICENSING OF GENOMIC INVENTIONS, 70 Fed. Reg. 18413, 18415 (April 11, 2005) (recommending careful consideration of where incentives are required and therefore when genomic inventions should be patented, and recommending licensing practices of such patents which facilitate full access to DNA sequences).

158. Timothy Caulfield et al., *Evidence and Anecdotes: An Analysis of Human Gene Patenting Controversies*, 24 NATURE BIOTECHNOLOGY 1091, 1093 (2006).

the Article demonstrates, such oversight may require familiarity with three separate areas of the law: patent, food and drug, and antitrust law.

The case study of Taxol in Part II has implications for effective government stewardship of its biomedical enterprise. Because of the significant federal investment in biomedical research, Congress has developed statutory mechanisms to transfer government research to the private sector for commercialization, but Taxol illustrates that technology transfer unaccompanied by public interest concerns can result in high barriers to patient access despite initial taxpayer funding. There are opportunities for government and citizen intervention when the patenting of government-funded research does not translate into reasonably available medical products, but significant political pressure is likely required to activate the generally dormant procedures that contemplate interference with existing patent rights in certain situations.

The recurring conflicts between brand-name and generic pharmaceutical companies over the rights to market therapeutically significant compounds emerge in this Article, as illustrated in Part II and Part III with respect to Taxol and Tamoxifen. The interface between intellectual property and antitrust law is highlighted by the enforcement actions from the FTC and the states when antitrust liability is identified by potentially anticompetitive arrangements between the brand-name and generic competitors. Although some Hatch-Waxman abuses have been curbed, more vigilance is needed to ensure that the contemplated transitions from brand-name to generic markets proceed without delay. These are issues for patients as well as third-party payers, as the cost of pharmaceuticals is often assumed by insurers, whether government (Medicare, Medicaid) or private.

As cancer research became informed by the insights of molecular biology, more recent controversies emerge over the patenting of therapeutic products developed from biotechnology. The patenting disputes over Herceptin, an antibody, and the BRCA1 and BRCA2 genes illustrate these dilemmas, as discussed in Part IV and Part V. Patent protection certainly accelerated the development of Herceptin as a new therapeutic, and although some patent infringement litigation has ensued, the patents remain in force and allow legitimate market dominance to date. However, the high price for Herceptin surely distinguishes the biologic therapeutic from more conventional treatments for breast cancer, and illustrates an emerging patent-related dilemma resulting from the success of biotechnology medicines. Due to its relatively recent origin, the biotechnology revolution in medicine has not yet generated reliable mechanisms to ensure that a generic market develops when initial patent protections elapse, and the acclaim for Herceptin will surely accelerate the attention to this issue. Here, patient advocates will need to monitor the vigor of the FDA as it responds to the demands for a generic approval process for biologics,

making sure that such a system can truly speed the development of generic alternatives, and that a regulatory process is not abused through patent strategies, as has been observed in the Hatch-Waxman context.

The patenting and resulting market dominance over the use of the BRCA1 and BRCA2 genes has significant consequences for the efforts to optimize genetic testing, as the patents have constrained the scientific research that could expand testing methodologies. These are access issues for researchers, initially, but the consequences are real for patients who may not receive the most accurate assessment of their genetic susceptibility to breast cancer. Other breast-cancer related genes will be identified by researchers, and the benefits and limitations of DNA patenting will continue to be debated. There are proposals for ensuring access to patented DNA sequences, such as a reasonable royalty structure or a direct research exemption, and these mechanisms may receive more attention as the pharmacogenomic era gets underway, which will greatly rely on genetic testing. Despite widespread public concern about the role of patents in mediating the availability of medical advances, there are significant differences between the United States and Europe in the availability of patent opposition procedures, illustrated by the legal challenges posed to the European patents on the BRCA1 and BRCA2 genes. U.S. patent law requires a robust patent opposition procedure, in order that all stakeholders, such as breast cancer patient advocates, have the option to challenge patents with legal defects.

Advocates for women's health have played a significant role in the patent issues discussed here, whether calling attention to abuses of the Hatch-Waxman generic approval process, litigating antitrust claims against collusive conduct by brand-name and generic companies, demanding access equity to high-priced biologics, or participating in the standard-setting for the granting of DNA patents. Continued progress in women's health research and meaningful access for women to medical advances are integral components of achieving full gender equity. To achieve these goals, it will be necessary for all concerned with women's health to maintain a sophisticated understanding of the role that intellectual property plays in the development and control of essential scientific and medical resources.¹⁵⁹

159. See Karen H. Rothenberg, *New Perspectives for Teaching and Scholarship: The Role of Gender in Law and Health Care*, 54 MD. L. REV. 473, 487 (1995) (addressing the need for feminist scholarship at the intersection of biomedical sciences and the law, noting that "fruitful legal and policy analysis incorporate empirical research, feminist theory, and interdisciplinary approaches").