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Case Supplement:
AstraZeneca, Prilosec, and Nexium

This case supplement explores some of the pharmaceutical regulation ground rules and how they manifest themselves in the game of market advantage.

Framing the Problem

In a situation similar to that of AstraZeneca and Prilosec in 2001, Eli Lilly's patents on Prozac (fluoxetine HCl), a multibillion-dollar antidepressant, were scheduled to expire in August 2001. The company expected to lose $1.5 to $2 billion in sales of the product per year following expiry. Schering-Plough's allergy drug, Claritin, which generated a third of the company's sales, would experience patent expiration in 2002.[1] Faced with such dramatic losses of revenue, firms employed a number of strategies to extend drug franchises. Many approaches were widely accepted, but others seemed like attempts to push market advantages as far as possible through creative interpretation of the regulations. Sometimes the drug firms prevailed; often, regulators intervened, but usually not before the firm had extended its *de facto* rights for critical months, recognizing substantial incremental revenues.

The Ground Rules: Exploring the Regulatory Environment

Before exploring franchise extension strategies, we should introduce two core components of the pharmaceutical regulatory regime: the Hatch-Waxman Act and the Orphan Drug Act.[2]

THE HATCH-WAXMAN ACT AND THE GENERICS

In 1984 the U.S. Congress transformed the rules of the game for generic drug makers (generics) with passage of the Drug Price Competition and Patent Term Restoration Act, or Hatch-Waxman Act. Under this legislation, the FDA granted an extension to the patent for time lost due to FDA drug review (Case Exhibit 2). The authorities determined the extension by how

[1] Amy Tsao, "The Fog Shrouding Schering-Plough," *BusinessWeek Online*, March 1, 2001, http://www.businessweek.com/bwdaily/dnflash/mar2001/nf2001031_945.htm (accessed June 2001).

[2] Note that discussion of the Hatch-Waxman Act appears in the AstraZeneca case. We provide it here in full text for those using this supplement as a standalone document.

long the drug spent in each phase of FDA trials, and the patent holder had to show promptness and due diligence during the trials process.

The average patent extension was two and a half to three years, with the maximum allowable extension being five years, or fourteen years from the date of original FDA approval, whichever was less. The FDA granted a five-year exclusivity for newly approved drugs regardless of the patent situation, which was particularly necessary for drugs nearing the end of their patent life at the time of approval.[3] Hatch-Waxman also brought about a three-year exclusive marketing period for an approved supplemental new drug application (SNDA) for a new indication of a drug. Thus, besides seeking new indications to expand the market, companies might wish to pursue new indications with clinical trials or formulations simply to get the three-year exclusivity. As a result, firms might decide to wait for the drug to near patent expiration to introduce a new indication, even though such approval might have expanded the market for the drug if introduced earlier.

Perhaps the most substantial impact of Hatch-Waxman was to expand the opportunities for generic drug makers. For the first generic to file and have its abbreviated new drug application (ANDA) approved, the Act gave six months of exclusive generic marketing rights following the expiration of the drug's patent protection. It also gave generic firms the freedom to test and manipulate patented drugs to develop a generic equivalent and seek FDA approval as long as they did not sell the product until after patent expiration. This limited the original patent-owning drug firms' power to sue for patent infringement. Generic drug makers could also file for approval if they showed that their product did not infringe other firms' patents or that a patent was invalid. This allowed generic firms to prepare FDA-approved, bioequivalent, generic versions of drugs for market introduction as soon as a patent expired or even earlier.

Since passage of Hatch-Waxman, generics captured an increasing percentage of the pharmaceutical market, up from less than 15 percent in the mid-1980s to more than 40 percent in 2000. As soon as competitors introduced generic alternatives, revenues and prices of the substituted products quickly dropped. Generics were priced based primarily on the costs to produce and sell drugs, while the pharmaceutical firms that originated the drugs had to also recover their massive R&D investments. As a result, generic firms effectively competed based on price.

THE ORPHAN DRUG ACT

The Orphan Drug Act of 1983 presented an important option for companies seeking to extend the exclusivity of therapeutics. According to the Act, a company could apply for orphan drug status for a therapy of a disease for which fewer than 200,000 patients had been diagnosed in the United States at the time of application. If approved, orphan drug status granted a firm seven years of exclusive sales rights, tax credits for R&D expenditures, and other incentives. Orphan drug status exclusivity could not be revoked unless a drug arose that was proven to demonstrate

[3] Exclusivity was granted upon approval of a drug product if the statutory requirements were met. Some drugs had both patent and exclusivity protection while others had just one or none. Patents and exclusivity might or might not run concurrently and might or might not encompass the same claims. Exclusivity was not added to the patent life. Thus, companies could only pursue various exclusivity strategies when the patent was near expiration to avoid overlap. FDA/Center for Drug Evaluation and Research, http://www.fda.gov/cder/ob/faqs.htm#What is the difference between patents and exclusivity? (accessed June 2001); Michael Strong, "FDA Policy and Regulation of Stereoisomers: Paradigm Shift and the Future of Safer, More Effective Drugs," *Food and Drug Law Journal* 54 (1999): 481, http://www.fdli.org/pubs/Journal%20Online/54_3/art%2011.pdf (accessed September 2000).

significantly improved efficacy relative to existing alternative treatments.[4] The European Union, Japan, Australia, and Singapore supported a similar policy.[5]

The intent of the Act was to encourage drug firms to pursue a niche business strategy and develop treatments for diseases and conditions suffered by a relatively small number of patients. Without the Act, many "orphan diseases" would not represent a large enough market for firms to recover R&D expenditures under the standard patent protection regime. Despite the relatively small number of patients to which individual orphan drugs might apply, orphan drugs could be quite profitable. For example, in 1999 Genzyme's treatment for Gaucher's disease, Ceredase (alglucerase), enjoyed annual sales approaching $500 million.[6]

A drug with a broad number of indications could also receive orphan protection for a disease subtype, assuming appropriate clinical trials. Bristol-Myers Squibb's cancer treatment, Taxol (paclitaxel), received orphan drug designation for the treatment of AIDS-related Kaposi sarcoma, a type of cancer. Amgen's Epogen received orphan drug status for chronic renal failure, but had since identified many other applications that created a multibillion-dollar drug. Protein drugs such as Epogen could particularly benefit from orphan drug status, as they were often prescribed for rare genetic defects in which a patient's system failed to produce necessary proteins.

Rules of the Game: Strategies to Extend Exclusivity of Drugs

Below we explore the most prevalent exclusivity extension strategies employed by pharmaceutical firms and their generic competitors.

FILING NOVEL PATENTS

A common extension strategy was to conduct ongoing research to discover new patentable capabilities, such as new means of manufacturing, formulating, or delivering a pharmaceutical. A firm might also conduct additional clinical trials to add new claims and uses for an existing drug (Case Exhibits 2 and 4). Furthermore, firms could seek patents for new combinations of therapeutics, generating a new indication and improved therapy, either through greater efficacy or milder side effects. Upon discovering the bacteria *H. pylori*'s responsibility for ulcers (Case Exhibit 7), AstraZeneca developed and patented a combination therapy using an acid pump inhibitor and an antibiotic. Additionally, Prilosec could be combined with anti-inflammatory drugs to offset potentially ulcer-causing side effects.

Firms could also patent new formulations of an existing drug. Pfizer patented a new formulation of its Neurotonin (gabapentin) epilepsy drug (estimated sales in 2001 of $1.5 billion) to prevent degradation after the basic use patent expired in 2000.[7] In fact, firms sometimes failed to identify and patent enough of the alternative forms and manufacturing techniques of their drugs, providing opportunities for competitors. The chemical structures of Prilosec and Prevacid

[4] R. Martin, D. Owens, and U. Wright, "Orphan Drug Designation for Lysosomal Storage Disease: A Biotechnology Intellectual Property War," available from Professor James Conley (Kellogg Graduate School of Management, Evanston, IL).

[5] "EU's New Orphan Drug Regulations," *Nature Biotechnology* 18 (June 2000): 582.

[6] J. Van Brunt, "The Payoff: Betting On Protein Drugs," *Signals Magazine*, June 24, 2000, http://www.signalsmag.com/signalsmag.nsf/0/49437A968EE454E188256907000E7ADC; S. Rossi and E. O. Teisberg, "Genzyme Corporation: Strategic Challenges with Ceredase," Case #9-793-120 (Harvard Business School Publishing, 1993).

[7] R. Langreth and V. Murphy, "Perennial Patents," *Forbes*, April 2, 2001, 52–53.

(lansoprazole) were quite similar. If AstraZeneca had patented other variations of Prilosec, Prevacid might not have arisen as a competitor (Case Exhibits 8 and 9 and **Exhibit CS1**).[8]

In a similar case with a different result, Eli Lilly hoped its patent on a Prozac variation compound, duloxetine, might help the firm deal with Prozac's loss of patent protection. Early clinical trials showed the compound offered superior antidepression properties, as well as possibly providing a treatment for urinary incontinence and pain.[9] Lilly also introduced a new once-a-week version of Prozac, called Prozac Weekly, for which it could receive protection.

Schering-Plough had multiple fallback patents for its blockbuster Claritin, scheduled to lose patent protection in December 2002. It had a patent licensed from Sepracor for an active metabolite (compound into which a drug is converted in the body)[10] of Claritin, which the firm hoped to market as Clarinex (desloratadine). While the Clarinex patent would expire in 2004, a method-of-use patent for specific therapeutic contexts (for example, seasonal allergic rhinitis) would not expire until 2014, assuming no successful legal challenges.[11] A commitment to ongoing R&D on existing products could yield many years of offset expirations and essentially "evergreen" the advantages of the original invention, albeit for smaller markets.

Companies such as Sepracor provided services to drug firms that involved finding new active metabolites, formulations, and therapeutic uses. Sepracor licensed its discoveries to drug firms to extend the market advantages of the original drug invention. In addition to drug metabolites, Sepracor developed pure forms of the drug molecule. Drugs often came as enantiomers, mirror images of the drug, rather than exact versions of the same molecule. These enantiomers might be the cause of many side effects (**Exhibit CS2**).[12] This method had not yet been shown to be completely effective. The purified version of Eli Lilly's Prozac seemed to cause more side effects than the original. Clinical trials had to be discontinued.[13]

In comparison to patenting new variations of a compound, the manufacturing process for a drug could provide an easier target. There were usually multiple options for manufacture of a given compound, and new manufacturing process patents could bypass existing process patents. As a result, drug firms should patent any viable manner that they discovered for fabricating a drug, not just the most efficient. Because of the high markup of patented therapeutics relative to manufacturing and sales costs—recall that bringing a drug to market represented the primary expense—generic firms might not require the most efficient means of synthesizing a drug in order to substantially undercut the price.

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[8] TAP Pharmaceutical Products, Inc., http://www.prevacid.com (accessed March 2001). A drug class or genus has a certain arrangement of atoms that allows it to have a therapeutic effect, but certain atoms can be replaced with others, which gives different variations or species within the genus. When patenting, it is necessary to cover both genus and species. Prevacid was a variation on the Prilosec arrangement of atoms.

[9] A. D. Westanmo et al., "Duloxetine: A Balanced and Selective Norepinephrine and Serotonin-Reuptake Inhibitor," *American Journal of Health-System Pharmacy* 62, no. 23 (2005): 2481–2490, http://www.medscape.com/viewarticle/518683.

[10] Typically by using the active metabolite as the drug's active ingredient, the drug becomes more specific and therefore more effective, safer, and/or usable at a lower dose.

[11] "Schering-Plough Files NDA for Desloratadine," Pharmalicensing Ltd., January 19, 2001, http://www.pharmalicensing.com/news/adisp/941150566_3818d166152a9 (accessed January 2001).

[12] Michael Strong, "FDA Policy and Regulation of Stereoisomers: Paradigm Shift and the Future of Safer, More Effective Drugs," *Food and Drug Law Journal* 54 (1999): 465, http://www.fdli.org/pubs/Journal%20Online/54_3/art%2011.pdf (accessed September 2000).

[13] S. Adams and R. Langreth, "But Did It Cure Cancer?" *Forbes*, January 8, 2001, 34.

Amgen was able to protect its anemia drug Epogen (epoetin alfa) with five manufacturing-process patents.[14] Process patents were often used in the case of biologics; how a protein was made could impact its properties. However, they were not included in the FDA's Orange Book, a listing of the patents a company had on a drug, used to determine when a generic could be approved by the FDA (Case Exhibit 2).

TAKING CHANCES WITH NOVEL PATENTS

Somewhat more questionable strategies for extending competitive advantage involved pharmaceutical firms submitting patents of tenuous novelty, or automatically suing generic drug makers for patent infringement, whether reasonable cause existed or not. Sometimes firms filed patent-seeking protection for trivial attributes, such as the color of the pill.[15] Despite appearing weak, firms had a rationale for such patent applications. Even if generic firms challenged such a patent's entry into the Orange Book, it would trigger the thirty-month delay in FDA approval of a generic alternative, pending court decision on the case. The drug company, meanwhile, continued to enjoy exclusivity for the product (**Exhibit CS3**).

SUING THE GENERICS

Drug firms sued for patent infringement whenever a generic firm filed an ANDA (Case Exhibits 2 and 8) prior to the expiration of any of its patents. Filing a suit activated the thirty-month delay in FDA approval of the generic (see Hatch-Waxman Act). Astra Pharmaceuticals, LP and Astra AB filed lawsuits in 1999 against Kremers Urban Development Company (KUDCO), Schwarz Pharma Inc., Cheminor Drugs, Ltd., and Reddy Cheminor, Inc. for patent infringement, triggered by the filing of an ANDA by KUDCO for generic omeprazole products in the United States.[16] These suits were still pending as of 2001. AstraZeneca continued the policy of suing any company seeking approval of a generic form of Prilosec, and also filed questionably "novel" patents on Prilosec.[17] In 2001 Senators Charles Schumer (D-N.Y.) and John McCain (R-Ariz.) submitted a bill seeking to limit the delay of generic drug introduction. Generally, the bill proposed to activate the thirty-month delay only with respect to cases asserting the patent on a drug's active ingredient, rather than any pertinent patent.[18]

PAYING THE GENERIC DRUG COMPANIES

Another questionable but commonly used strategy to maintain market exclusivity was for pharmaceutical companies to pay the generic companies to delay introduction of competing drugs. In some forms, this appeared to be legal, if unfortunate for competition. Bayer paid Barr Labs $28 million a year to drop the patent challenge for its antibiotic Cipro (ciproflaxin, annual sales of $1 billion), whose patent would expire in December 2003. Various forms of the practice seemed to skirt legality. Abbott Laboratories, Schering-Plough, and Aventis reportedly paid generic firms millions to discourage or at least delay the introduction of versions of their best-

[14] A. Pollack, "Two Paths to the Same Protein," *New York Times*, March 28, 2000; L. Johannes and R. L. Rundle, "Amgen Wins a Round, as Judge Rules Transkaryotic Is Infringing Its Patent," *Wall Street Journal*, April 27, 2000.

[15] Note that the Purple Pill property was protected by trade dress, not a patent. This represented a use of intellectual property protection clearly consistent with legal intent, as opposed to seeking a *patent* for the color of a pill.

[16] BioSpace Beat, http://www.biospace.com/news_company.cfm?CompanyID=1774 (accessed July 2001).

[17] "AstraZeneca PLC: Suit Alleges Move by Andrx Will Infringe Prilosec Patent," *Wall Street Journal*, May 7, 2001. There sometimes is a valid case for the lawsuits in that in order to develop a generic the company had to infringe the original manufacturer's patent(s).

[18] Lisa Richwine, "Bill Introduced to Stop U.S. Generic Drug Delays," Reuters, May 1, 2001, http://dailynews.yahoo.com/h/nm/20010501/sc/health_generics_dc_1.html (accessed May 2001); "Speedier Generics?" *BusinessWeek*, May 14, 2001, 59.

selling drugs.[19] In the case of Schering-Plough and its potassium chloride supplement K-Dur (potassium chloride), the company had already used the delay-triggering lawsuit strategy. The firm made payments in a settlement deal with generic firms that allowed a generic to be introduced two years before the patent expired in return for not challenging the patent's validity or seeking to bypass the patent. Additional payments were allegedly made disguised as licensing payments for unrelated products.

AstraZeneca had also been involved in similar activities over a breast cancer drug, tamoxifen. A generic firm challenged AstraZeneca's patent on tamoxifen in court. AstraZeneca agreed to sell the drug at a discount to the generic, which in turn sold the drug at a slight discount to market of 5 to 15 percent. AstraZeneca had since successfully defended its patent against four other generic manufacturers that sought to challenge it.[20] The Federal Trade Commission (FTC) had since begun cracking down on such activity, claiming the exercise of antitrust laws. Tellingly, drug firms appeared to continue this practice, suggesting the rewards outweighed the risks.[21] Such deals were also targets of the bill introduced by Senators Schumer and McCain.

CORNERING KEY INGREDIENTS

Generic drug companies also pushed regulations to the limit and beyond. Mylan Laboratories, a generic manufacturer, cornered the supply for key ingredients necessary to produce two antianxiety drugs. The FTC charged the firm with anticompetitive practices, a challenge for which Mylan settled by paying $100 million from the profits of the two drugs. In making its Gaucher's Disease drug, Ceredase (alglucerase), Genezyme executed an exclusive contract with the only supplier of placental tissue, located in Paris, providing *de facto* exclusivity on the drug. Though such a strategy might still draw fire from the FTC, anticompetitive charges could be bypassed with skillful political lobbying if a firm could show applicability of the Orphan Drug Act.

In order to counteract criticism of such practices, Genzyme employed a policy of transparency. The CEO invited a number of politicians to visit the company to address any concerns about the firm's practices.

Besides the FTC's oversight activities, consumer groups began filing suits seeking class action status, such as in the case of Bristol-Myers Squibb's BuSpar (buspirone, Exhibit CS3).[22] At Congress's behest, the FTC announced a study of the delaying tactics of pharmaceutical firms.[23] This action had the potential to mark the beginning of a round of legislation seeking to limit the use of questionable patent extension strategies.[24] Regardless of future changes in legislation

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[19] David Brinkerhoff, "Drug Conspiracy Charge for Andrx, Aventis," Reuters and Yahoo, Inc., May 14, 2001, http://dailynews.yahoo.com/h/nm/20010514/bs/health_generics_suit_dc_4.html (accessed May 2001); R. Gold, "Aventis Is Sued Over Alleged Payments," *Wall Street Journal*, May 15, 2001.

[20] G. Harris, "Group Sues Barr, AstraZeneca, Citing Tamoxifen Price Collusion," *Wall Street Journal*, May 10, 2001.

[21] J. R. Wilke, "Schering-Plough to Face Antitrust Charge," *Wall Street Journal*, April 2, 2001; M. Wigfield and J. R. Wilke, "Schering-Plough Plans to Contest Lawsuit Alleging Illegal Payments," *Wall Street Journal*, April 3, 2001.

[22] G. Harris and R. Rundle, "Watson, Mylan Suits Target FDA Over Drug Patent of Bristol-Myers," *Wall Street Journal*, December 1, 2000; G. Harris, "Bristol-Myers Faces Consumer Lawsuits Involving BuSpar," *Wall Street Journal*, April 10, 2001; V. Murphy, "High Anxiety," *Forbes*, April 30, 2001, 32.

[23] "White House Won't Block FTC Generic-Drug Study," *Wall Street Journal*, April 19, 2001; "Protection Racket," *The Economist*, May 19, 2001, 58.

[24] J. Greenwald, "RX for Nosebleed Prices," *Time*, May 21, 2001, 42–43; J. Carey, "Costly Drugs: An Even Bloodier Backlash Ahead," *BusinessWeek*, May 28, 2001, 40.

and/or enforcement, drug firms would continue to push the limits of regulation as long as they perceived the outcomes of such behavior to be profitable, on balance, and favorable.

IDENTIFYING DISEASE SUBTYPES AND THE FIELD OF PHARMACOGENOMICS

Medical science's increasing understanding of human genetics offered unique implications for extending exclusivity protection. Many diseases turned out to have several subtypes as defined by medical experts, some of which were linked to mutations in the gene or genes that led to a particular disease. Human genetic variation could also manifest in varied effectiveness and/or side effect reactions of the same drug between patients. The study of these genetic-based phenomena was called *pharmacogenomics*.[25] It might be possible to receive a new patent for a drug by relating its effectiveness to certain genetic markers or by claiming a new method of use for a certain disease subtype. These alternatives might qualify for three-year exclusive rights under the Hatch-Waxman Act.

Moreover, major diseases with more than 200,000 afflicted individuals in the United States could potentially be broken down into multiple orphan disease subtypes, each representing less than 200,000 sufferers. A drug might then gain additional exclusivity if it could target a disease subtype under the Orphan Drug Act. However, employing such a tactic would only protect a drug for a narrow disease indication unless the target disease could be broken down into several subtypes, each qualifying for orphan status. The drug would still need to be proven effective in each case, as well as be the first such therapeutic for the disease subtype in question to qualify for orphan drug status.

CONDUCTING PEDIATRIC STUDIES

Many drugs were tested in adults only. Doctors often prescribed drugs for children at lower doses without having evidence from clinical trials of any differential impacts of the drug between children and adults. Such prescriptions could produce unexpected, harmful side effects.

To encourage companies to conduct trials on the pediatric population, the FDA granted a six-month extension of exclusivity on a drug for which a firm collected clinical pediatric information. (Of course, the disease had to occur in children for the company to receive the extension.) Eli Lilly acquired such an extension for its blockbuster Prozac, helping it earn an additional billion dollars as a result of extended exclusivity. On May 2, 2001, AstraZeneca received the six-month extension on its patents (with protection since extended to April 2002) for completing clinical studies in children for Prilosec, as well as for providing guidance for use of the drug in children.[26] Furthermore, orphan drug status could pertain to drugs shown to treat pediatric versions of a disease with fewer than 200,000 child sufferers.

PETITIONING PATIENTS, DOCTORS, AND CONGRESS

Drug companies might also petition Congress to extend a drug's patent life. The law stated that Congress could extend the life of any patent; however, congressional grants of extension required a justifiable, substantial reason beyond profits. Congressional extensions had been granted for some drugs in a firm's "pipeline" for which an NDA was submitted to the FDA

[25] J. B. Lichter and J. H. Kurth, "The Impact of Pharmacogenetics on the Future of Healthcare," *Current Opinion in Biotechnology* 8 (1997): 692–695; A. Marshall, "Laying the Foundations for Personalized Medicines," *Nature Biotechnology* 15 (October 1997): 954–957; A. Marshall, "Getting the Right Drug into the Right Patient," *Nature Biotechnology* 15 (November 1997): 1249–1252.

[26] AstraZeneca, http://www.astrazeneca-us.com/news/article.asp?file=2001050201.htm (accessed June 2001).

during passage of the Hatch-Waxman Act. The Act originally limited these drugs to two years of patent term restoration in the belief that they would soon be approved. However, the drug companies argued that the approval process in some cases took eight years, as was the case with Claritin.

Congress had given relief to some petitions for other drugs such as forane, glyburide, Lopid (gemfibrozil), and Daypro (oxaprozin), as well as the food additives aspartame and olestra. In light of the controversy surrounding patented drug prices, it was unlikely that Congress would grant any more substantial patent extensions in the near future. Schering-Plough's lobbying efforts on behalf of Claritin since 1996 had been unsuccessful. Consumer rights groups seized the opportunity to criticize the company for its lobbying efforts for a drug that had proven so lucrative.[27] Claritin already received a three-year patent extension as a result of General Agreement on Trade and Tariffs (GATT) legislation. In this legislation, the United States agreed to follow the global norm of twenty-year patent terms after the date of filing, rather than seventeen years after the date of issue. In another case, American Home Products was able to block generic competition for Premarin (conjugated estrogens), a blockbuster hormone replacement therapy ($1.84 billion in 2000 U.S. sales)[28] whose patent expired decades ago, by lobbying Congress and coordinating citizen's petitions to the FDA. In an unclear and contested claim, the lobbyists and petitions asserted the generic was not the bioequivalent of Premarin and could thus cause harmful effects.[29]

INTRODUCING A GENERIC

Recently, some pharmaceutical firms had begun introducing their own generic substitutes prior to patent expirations while concurrently raising the prices of the standard versions, attempting to maximize pre-expiration profit from brand-loyal customers. The generics captured more price-sensitive customers prior to the introduction of competing generics. The practice positioned the firm to combat other generics after patent expiration, and it appeared to increase the producer's total profits at the expense of the generic firms.[30]

GOING OVER THE COUNTER

The FDA sometimes allowed drugs with proven high safety to be available without a prescription over the counter (OTC), usually at a lower dose. In order to achieve OTC status, a firm had to petition the FDA, and the target disease had to be diagnosable and treatable without consulting a doctor. As of 2001 AstraZeneca had submitted an OTC petition for Prilosec that would likely satisfy the FDA's criteria. The older classes of H_2 blockers and antacids had both converted to OTC versions.

LICENSING TRADEMARKS AND UNEXPIRED PATENTS

Even after a drug's primary patent expired, options still existed to extract value from unexpired patents on other aspects of the product, such as production, formulation, or trademarks.

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[27] J. Harwood and L. McGinley, "Bradley, Stepping Up Attacks on Gore, Says He 'Abandoned' Health-Care Goal," *Wall Street Journal*, November 9, 1999.

[28] S. Hensley, "American Home Products Boosts Its Research Efforts," *Wall Street Journal*, May 17, 2001.

[29] Citizens Against Government Waste, http://www.cagw.org/publications/lookinglass/pubs.looking.Premarin.htm (accessed April 2001).

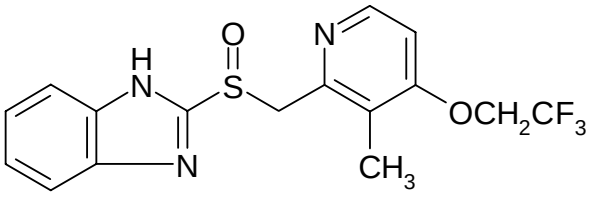
[30] M. I. Kamien and I. Zang, "Virtual Patent Extension by Cannibalization," *Southern Economic Journal* 66 (1999): 117–131.

Trademarks offered more limited intellectual property protection than patents, but persisted indefinitely.

Licensing the additional intellectual property related to a patent-expired drug to a generic firm placed the generic in a position more akin to a contract manufacturer than a competitor. Licensing production-process patents for a drug allowed the generic licensee to produce the exact same drug with the same efficiency as the formerly patented product. Identical production guaranteed bioequivalence for ANDA approval, eliminating the cost of additional tests. Process patent licensing also allowed the licensor to extract some value from patents that generic firms might otherwise bypass by alternative production methods.

Since generic firms did not as a rule build significant product brands, it might also be of value for pharmaceutical companies to license patent-expired products' trademarks to a generic firm. In this manner the generic firm could maintain the brand and trademark, potentially providing a marketing advantage over other generics. Likewise, a drug firm could license its overall corporate trademark as a sign of quality for use by select generics. This required the company to have a well-known public identity.

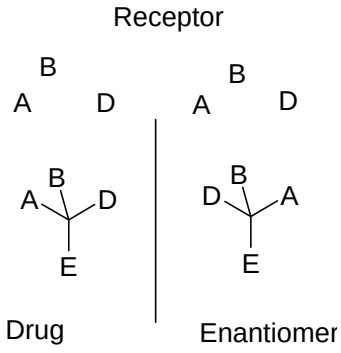
Exhibit CS1: Prevacid Delayed-Release Capsules Active Ingredient



The active ingredient in Prevacid (lansoprazole) delayed-release capsules is a substituted benzimidazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulfinyl] benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_3N_3O_2S$ with a molecular weight of 369.37. Lansoprazole is a white to brownish-white odorless crystalline powder that melts with decomposition at approximately 166°C. Lansoprazole is freely soluble in dimethylformamide; soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyl acetate, dichloromethane, and acetonitrile; very slightly soluble in ether; and practically insoluble in hexane and water. Lansoprazole is stable when exposed to light for up to two months. The compound degrades in aqueous solution, the rate of degradation increasing with decreasing pH. At 25°C the $t_{1/2}$ is approximately 0.5 hour at pH 5.0 and approximately 18 hours at pH 7.0.

Prevacid is supplied in delayed-release capsules for oral administration. The delayed-release capsules contain the active ingredient, lansoprazole, in the form of enteric-coated granules and are available in two dosage strengths: 15mg and 30mg of lansoprazole per capsule. Each delayed-release capsule contains enteric-coated granules consisting of lansoprazole, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide.

Exhibit CS2: Enantiomer Drug



An enantiomer of a drug is the mirror image of it. A different molecule from the drug, an enantiomer may not bind to the proper receptor, potentially causing side effects. By removing enantiomers, a drug should become more specific and therefore more effective, safer, and/or effective at a lower dose.

Exhibit CS3: Bristol-Myers Squibb and Novel Patents

Bristol-Myers Squibb received an additional patent on its antianxiety drug BuSpar (buspirone, annual sales in 2000 of $709 million) one day before the main patent was due to expire, after fourteen years on the market. The patent covered a metabolite of the drug produced in the liver. The company contended that the metabolite was largely responsible for the antianxiety effect, so the new patent covered the administration of the drug. A generic would infringe the patent when digested by the body. As such, Bristol-Myers Squibb requested the FDA list the patent in the Orange Book.

While the companies went to court, regulators froze approval for the generic, to be marketed by Watson Pharmaceuticals and Mylan Pharmaceuticals. The law stated that the FDA, which usually agrees to requests for Orange Book entry due to a lack of expertise in patent evaluation, had to freeze approval for generic drugs for up to thirty months unless the case was settled in court before this (effectively extending the exclusivity of a drug). Had Bristol-Myers Squibb's patent been received one day later, it would have been too late. After consideration, a federal judge ruled that the generic be sold because the company misrepresented the scope of the patent to the FDA. By then Bristol-Myers Squibb had already sold an additional $200 million of BuSpar, far surpassing the cost of legal action.[31]

In another case, Bristol-Myers Squibb delayed a generic for its anticancer drug, Taxol (paclitaxel), for almost three years by suing generic manufacturers for patent infringement. The firm received the patents in question after the main Taxol patent had expired, adding several billion dollars in additional sales. Many of these later patents held key provisions later ruled invalid by a federal judge.[32]

The courts invalidated a key Eli Lilly patent on Prozac that covered how the drug works in the brain. The patent could have had extended protection through August 2003. Instead, exclusivity ended with the expiration of the pediatric trials extension in August 2001.[33] The invalidated patent and the ensuing legal actions failed to provide Lilly with additional exclusivity.

[31] G. Harris, "Judge Permits Cheap Knockoff of Bristol Drug," *Wall Street Journal*, March 14, 2001.

[32] http://www.msnbc.com/news/376731.asp?0m=B20A.

[33] Jed Seltzer, "Court Affirms Decision Allowing Generic Prozac," Reuters and Yahoo, Inc., May 30, 2001, http://biz.yahoo.com/rf/010530/n30447528_7.html (accessed June 2001).