INTERNATIONAL
BioPharm
The Science & Business of BioPharmaceuticals

Strategies for Extending the Life of Patents

To maximize patent term, seek patent protection for new formulations, new methods of use, and potential combination products.

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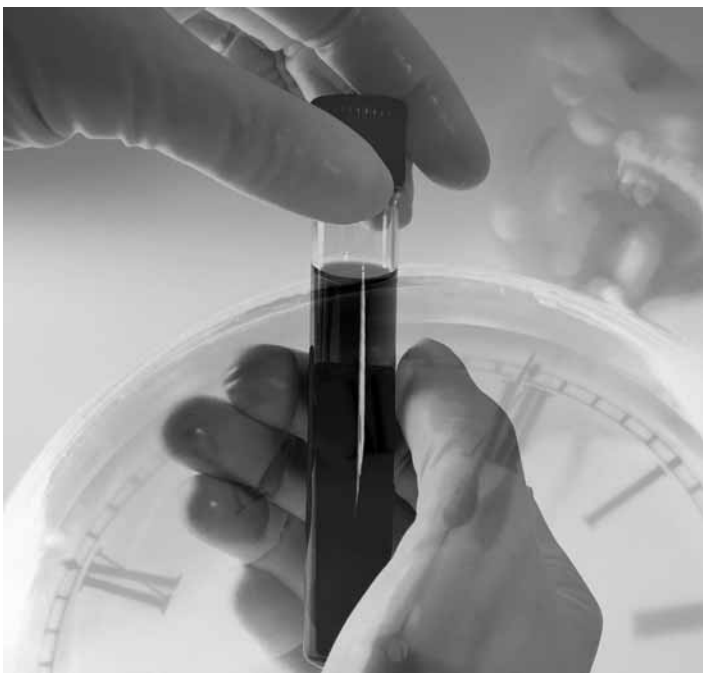

Pharmaceutical companies today are faced with increased costs for drug discovery and development and aggressive competition from generic drug companies. As research costs skyrocket, generic drug companies sit poised and ready to compete as soon as a patent expires. Maximizing patent term for successful products is an effective strategy for fending off generic competition and extending product lifecycle. This article will explore strategies for keeping a product under the patent umbrella.

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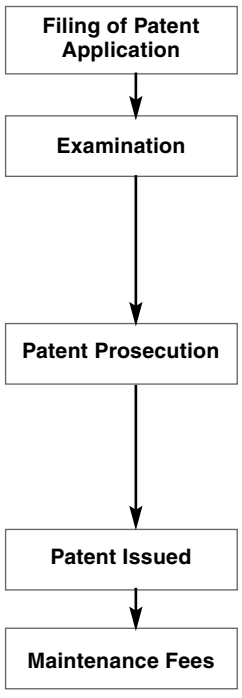
RISING COSTS OF DRUG DEVELOPMENT

The costs associated with discovering a compound, turning that discovery into a suitable drug candidate, and getting that candidate to market have risen dramatically. Some estimates indicate that the cost for developing and marketing a single pharmaceutical product has risen from $54 million in the 1970s to greater than $800 million by 2000.[1]

Patent protection and the market exclusivity that comes with it help to ensure a return on investment. A patent holder has the right to exclude others from making, using, and selling the patented invention for a defined period (Figure 1). Therefore, patented drugs are temporarily safe from the competition of generics, often resulting in substantial revenues. For example, US sales for Prilosec in 2000 were over $4 billion,[2] and worldwide sales of on-patent Lipitor and Prevacid totaled over $9.2 billion and $2.5 billion, respectively, in 2003.[3,4]

Over the next few years, a remarkable number of patented "blockbuster" drugs will lose their protection (Table 1). When Eli Lilly's patents for Prozac (fluoxetine) expired in 2001, the concomitant multi-

Figure 1. U.S. Patent Application Process.[9]



A registered patent attorney/agent or an inventor acting *pro se* files a utility patent application with the United States Patent and Trademark Office (USPTO).

A USPTO Examiner with technical training in the field of the invention conducts a prior art search and determines whether the application satisfies the legal requirements for patentability.

The Examiner issues an "office action" setting forth the grounds for rejection. The Applicant or her representative responds by amending the claims, submitting arguments, or doing both to overcome the Examiner's rejections. The Examiner reviews the response and 1) allows the claims or 2) issues another office action. This "back-and-forth" with the USPTO continues until the Examiner issues a "Notice of Allowance" or the Applicant abandons the application. If necessary, the Examiner's decision may be appealed to the Board of Patent Appeals and Interferences and then to a federal court.

Issuance of the patent confers on the Applicant the right to exclude others from making, using, or selling the claimed invention for a term of 20 years from the date the earliest application was filed.

Patent rights are maintained by the payment of maintenance fees at 3.5, 7.5, and 11.5 years from the issue date.

million dollar losses in revenue demonstrated the devastating impact of patent expiration. Table 2 shows three examples of revenue losses following patent expiration.

Pharmaceutical companies can employ a number of strategies to maximize patent protection on important compounds, thereby maximizing the commercial lifecycle. During the research and development phase of drug discovery, a company will typically obtain patent protection for the general compound and likely a method of using the compound in the treatment or prevention of a particular disease or condition. Often, additional patents can be obtained to effectively extend patent term and market exclusivity.

Once a compound or pharmaceutical composition has been patented, that patent becomes a prior art reference that must be considered when seeking additional patent protection around the compound or pharmaceutical. As a result, the new patent protection generally encompasses narrow improvements or new uses for the pharmaceutical not disclosed or suggested in the original patent. Strategies for maximizing patent term are summarized in Table 3.

NEW FORMULATIONS

One means for extending patent protection for a commercially successful drug is to obtain additional patents covering new formulations of the known compound. Developing and patenting new formulations that promote patient compliance through reduced dosing or ease of use, or that exhibit improved therapeutic outcomes or more-favorable side-effect profiles, is particularly advantageous for defending against generics and protecting market share. Moreover, new formulations, as long as sufficiently similar to the original approved drug, have the additional advantage of a shorter FDA approval route.

Examples include sustained-release formulations of existing drugs. When Lilly was faced with the expiration of its patent for the blockbuster anti-depressant drug Prozac, the company developed and obtained patent protection and FDA approval for a once-weekly, sustained-release fluoxetine formulation. Bristol-Myers Squibb also obtained patent protection and FDA approval for its extended-release formulation of the diabetes drug Glucophage (metformin hydrochloride). Marketed under the brand name Glucophage XR, this new formulation permits once-daily dosing for Type II diabetics.

Additional patent protection can also be obtained around new formulations that permit new routes of administration for known drugs. The migraine treatment Imitrex (sumatriptan) accounts for more than $1 billion in annual sales for GSK.[5] The patent directed to the original compound is set to expire in 2006, so in an effort to extend patent protection and maintain its market share, GSK has developed and obtained FDA approval and patents directed to Imitrex formulations for intranasal delivery.

Table 1. Blockbuster Drugs Facing Patent Expiration[10, 11, 12]

Brand Name	Manufacturer	Revenues in 2002 (billions)	US Patent Expiration
Zocor	Merck	$6.2	2005
Zoloft	Pfizer	$2.9	2005
Ambien	Sanofi	$1.5	2006
Paxil	GlaxoSmithKline	$3.3	2006
Oxycontin	Purdue Pharma	$1.5	2006
Pravachol	Bristol Myers Squibb	$1.5	2006

Table 2. Revenue Losses Following Patent Expiration and Generic Drug Entry[13-16]

Brand Name	Manufacturer	US Sales (pre-patent expiration)	US Sales (post-patent expiration)	Year Expired
Claritin	Schering-Plough	>$3 billion	$370 million	2002
Prozac	Eli Lilly	>$2.9 billion	$480 million	2001
Pepcid	Merck	$755 million	$110 million	2000

STEREOSELECTIVITY

Drug manufacturers have also successfully exploited the stereoselectivity of drug action in developing single-enantiomer versions. Most active drug compounds are chiral — meaning the compound can exist in at least two structural forms in which the spatial arrangements are mirror images of each other. These two compounds are enantiomers and are chemically identical except for their molecular orientation in 3-D space. Single-enantiomer versions of drugs often have the advantage of increased efficacy and reduced side effects.

One of the success stories for exploiting chirality is Prilosec (omeprazole). The basic patent for this blockbuster acid-reflux drug expired in 2002. In an effort to retain its share of the lucrative gastrointestinal drug market, AstraZeneca began searching for a "better" omeprazole years before the patent was set to expire. The result was the synthesis of the single (S)-enantiomer of omeprazole, esomeprazole, which exhibits superior clinical efficacy and better bioavailability than the original drug. Esomeprazole is marketed as Nexium for the treatment of acid-reflux disease and accounted for nearly $3 billion in sales in 2003.[6]

NEW USES

In addition to patent protection for the original compound and method of use, patents directed to new uses and treatment indications can be obtained. Developing new methods of use for identified compounds can be a successful strategy for maximizing research dollars and for increasing the commercial life.

Several pharmaceutical companies have successfully obtained patent protection for new methods of use. For example, Merck originally developed, patented, and marketed finasteride as a treatment for benign prostate enlargement under the brand name Proscar. Additional patent protection and FDA approval were sought when a new use for finasteride — treating male pattern baldness — was identified. Finasteride for the treatment of hair loss is marketed under the brand name Propecia. Similarly, the compound atomoxetine was patented in the early 1980s by Lilly and initially investigated as a treatment for depression. Further research and development of atomoxetine led to the identification of a new use for this compound in the treatment of attention deficit hyperactivity disorder. Lilly has obtained patent protection and FDA approval for this new use, marketing it as Strattera. More than two million prescriptions for Strattera were written in its first nine months on the market.[7]

Ideally, more than one of these approaches should be employed to extend patent protection. For example, in addition to developing a once-weekly formulation, Lilly sought to minimize its losses from the expiration of the Prozac patent by obtaining a patent and FDA approval for a new medical use of fluoxetine in the treatment of premenstrual dysphoric disorder (PMDD). Lilly markets fluoxetine for PMDD as Sarafem and has secured patent protection until 2007 for this new indication.

Bupropion, the GSK drug that was reformulated into a sustained-release formulation, was also shown to aid in smoking cessation. GSK has secured additional patent protection for this new indication and for pharmaceutical formulations for this new use, which GSK markets under the brand name Zyban. Therefore, by developing and patenting both new formulations and new uses for known drugs, Lilly and GSK have enhanced their opportunities for maximizing patent protection for these drugs.

COMBINATIONS

Lilly has FDA approval and an active patent for olanzapine (Zyprexa) to treat schizophrenia. As noted above, the patent for the FDA-approved drug fluoxetine (Prozac) for treating depression has expired. To extend the life cycle of Zyprexa and to recoup losses due to the market entry of generic fluoxetine, Lilly has developed and patented a combination product called Symbyax for the treatment of bipolar disorder, comprising olanzapine and fluoxetine. Zyprexa accounted for more than $1 billion

Table 3. Strategies for Extending Drug Commercial Lifecycle

New Formulations	Exemplary Drugs
Sustained-release formulations	Once-weekly Prozac, WellbutrinXL, GlucophageXR
New routes of administration	Imitrex (intra-nasal delivery)
Chiral-switching	Nexium
New Treatment Indications	Proscar, Strattera
Combination Products	Symbyax, Combivir, Trizivir, Glucovance

in sales in 2003, and the combination product Symbyax is expected to add $100 million in sales to the Zyprexa product line.[8]

Developing treatments for HIV infection has been a research focus of GSK for two decades. GSK owns patents directed to pharmaceutical formulations of AZT, lamivudane, and abacavir sulfate, which it markets as individual products under the brand names Retrovir, Epivir, and Ziagen, respectively. All patents directed to pharmaceutical formulations comprising AZT alone will expire in early 2005. To extend its AZT line of products beyond the basic patent terms, GSK obtained additional patents directed to AZT in combination with its other HIV drugs. GSK markets the combination of AZT and lamivudane under the brand name Combivir for the treatment of HIV infection. A second combination of AZT, lamivudane, and abacavir sulfate is sold as Trizivir. Combivir and Trizivir together generated more than $1 billion in sales in 2003.[6]

In summary, it is critical to devise strategies for maximizing patent protection and product lifecycle early in the development process. In order to maximize patent term, companies should consider seeking patent protection for new formulations, new methods of use, and potential combination products even before launching the original product. Such strategies must be developed before patent expiration and prior to the imminent market entry of generic competitors. ◆

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