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J Pharm Bioallied Sci. 2010 Jan-Mar; 2(1): 2–7. PMCID: PMC3146086
doi: 10.4103/0975-7406.62694

Patent protection strategies

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Received January 25, 2010; Revised February 15, 2010; Accepted February 25, 2010.

Abstract

It is widely recognized that the pharmaceutical industry faces serious financial challenges. Large numbers of blockbuster drugs are losing patent protection and going generic. The pipeline of new drugs is too sparse to fill the gap and generate a platform for future growth. Moreover, many of the new products are biologics with much narrower target patient populations and comparatively higher prices relative to traditional pharmaceuticals. So now the time has come for pharmaceutical scientists to have a better understanding of patent fundamentals. This need is illustrated by analyses of key scientific and legal issues that arose during recent patent infringement cases involving Prozac, Prilosec, and Buspar. Facing this scenario, the pharmaceutical industry has moved to accelerate drug development process and to adopt at the same time different strategies to extend the life time of the patent monopoly to provide the economic incentives and utilizing it for drug discovery and development. This review covers the need of patent protection and various strategies to extend the patent.

Keywords: Expiration, patent, pharmaceutical, racemate, strategies

A patent is a legal device that grants an inventor market exclusivity over a new invention or medication. Market exclusivity can mean tremendous economic rewards for the patent holder because it provides the inventor with a monopoly over the invention for the 20-year patent term. Obtaining a patent and retaining market exclusivity can be a treacherous process, especially in the arena of pharmaceutical patents. Pharmaceutical companies today are facing increased costs for drug discovery and development and aggressive competition from generic drug companies [Table 1]. As research costs skyrocket, generic drug companies sit poised and are ready to compete as soon as a patent expires [Table 2]. Maximizing patent term for successful products is an effective strategy for fending off generic competition and extending product lifecycle. Patents grant the creators of new inventions exclusive control and possession over these inventions. This allows the inventor to prevent others from commercially using ideas or inventions without the creator's permission during the life of the patent.[1] Scientific, legal, and practical considerations must be carefully weighed to best protect an inventor's rights. Creating and protecting or attacking pharmaceutical patents requires close interaction between pharmaceutical scientists and lawyers. It also requires a good understanding of key concepts of each other's discipline. Therefore, there should be collaboration between scientists and attorneys.[2,3]

The division of labor can be summarized as ‘Scientists invent, Lawyers patent.’ However these two groups do not communicate effectively because there is a general lack of understanding of each culture, and these interactions often lead to a cognitive friction that is both disturbing and costly to the society.[4]

Market Exclusivity

The quest for market exclusivity[1] is the engine that drives patent legislation and litigation. Market exclusivity describes the crucial period of time, usually 20 years, when an entity enjoys an economic monopoly on its invention. These two decades of market exclusivity can bestow huge economic rewards for any inventor, and are extremely critical to the success of pharmaceutical companies in both profitability and recuperating invested capital. Market exclusivity also provides a vital incentive for continued development of new inventions. Without patent protection, the pharmaceutical company is unlikely to invest the capital needed to develop innovative medications. Diminished patent protection will reduce innovative desire to develop new and potentially better drugs and treatments, which in turn could result in the use of more expensive treatments. Market exclusivity has become even more critical in recent years due to a decline in innovative theories and formulations. For instance, pharmaceutical innovation has drastically declined and is concurrent with an extreme escalation in research costs. In turn, skyrocketing research costs have resulted in an increased dependence on market exclusivity as a means of maintaining growth and profitability.

Rising Costs of Drug Development

The costs associated with discovering a compound, turning this discovery into a suitable drug candidate, and getting it 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.[5] 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. Therefore, patented drugs are temporarily safe from the competition of generics, often resulting in substantial revenues. For example, US sales of Prilosec in 2000 were over $4 billion[6] and worldwide sales of on-patent Lipitor and Prevacid totaled over $9.2 billion and $2.5 billion, respectively, in 2003.[7] During the last couple of years, a remarkable number of patented ‘blockbuster’ drugs lost their protection [Table 3]. When Eli Lilly's patents for Prozac (Fluoxetine) expired in 2001, the concomitant multimillion dollar losses in revenue demonstrated the devastating impact of patent expiration.

The process of obtaining a patent begins when an inventor files a patent application in the United States Patent and Trademark Office (USPTO).[3] It is important to file a patent application as soon as practicable because the first person to file gains priority over all others who claim rights to the same invention. The application describes the invention, gives examples of how it can be used, and usually includes illustrations like schematic drawings or graphs. Filing swiftly and also thoroughness are important. The inventor cannot add new information once he or she has already filed a patent application. Figure 1 illustrates the patent application process. A registered patent attorney/agent or an inventor acting *pro se* files a utility patent application with the 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 his/her representative responds by amending the claims, submitting arguments, or doing both to overcome the rejections. The reviews the response and (1) allows the claim 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 patents confers on the applicant the right to exclude others from making, using, selling the claimed invention for 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.

Strategies for Extending Drug Commercial Lifecycle

A company intending to market a generic version of a listed drug must certify one of the following regarding the patents listed in connection with the innovator's New Drug Application NDA[6,7]: (1) It has not been patented; (2) the applicable patent has expired; (3) the patent will expire on a given date and that the generic version will not be marketed before that date; or (4) the listed patent is not infringed

or invalid. The generic company is also required to notify the innovator about the abbreviated NDA (ANDA) filing and explain the reasons why it believes the generic version will not infringe the listed patent or the listed patent is invalid.

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 a method likely to be used with the compound in the treatment or prevention of a particular disease or condition. 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 described below briefly.

New formulations

One means of extending patent protection for a commercially successful drug is to obtain additional patents covering new formulations of the known compound clinically superior to the previous drug formulation. 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 being sufficiently similar to the original approved drug, have the additional advantage of a shorter Food and Drug Administration FDA approval route.

Examples include sustained-release formulations of existing drugs. When Lilly faced the expiration of its patent for the blockbuster antidepressant 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.[8]

New routes of administration for known drugs

Additional patent protection can also be obtained for new formulations that permit new routes of administration for known drugs. The migraine treatment drug Imitrex (Sumatriptan) accounts for more than $1 billion in annual sales for GlaxoSmithKline [GSK]. 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.[9]

Stereoselectivity/chiral switches

Two thirds of the drugs presently in the market are chiral drugs, which means that of the two forms one is good the other is ineffective or even dangerous.[10] An additional issue has recently emerged involving enantiomeric drugs (drugs made up of two mirror-image molecules that have the same chemical composition) derived from racemate pharmaceuticals for which a company already holds a patent.[11] Many drugs are compounds made up of different mixtures of stereoisomers, and such mixtures can consist of either enantiomers or isomers. A ‘racemate’ or ‘racemic mixture’ is a compound consisting of an equal mixture of pairs of enantiomers. Many companies holding a patent nearing expiration for a racemic drug choose to remarket the drug as a single enantiomer under a different patent. This process of ‘racemic switching,’ allows drug companies to apply for FDA approval of the enantiomer, before the expiration of the racemic patent, while maintaining market exclusivity for the drug as a whole. Due to the fact that the enantiomer pharmaceutical sales reached $160 billion in 2002, racemic switching has become another valuable topic of discussion in the biotech patent arena[12] [Table 4].

Potential advantages of single enantiomer products

There are several advantages of single enantiomer products.[13] Some of them are (1) less complex, more

selective pharmacodynamic profile, (2) potential for an improved therapeutic index, (3) less complex pharmacokinetic profile, (4) reduced potential for complex drug interactions, and (5) less complex relationship between plasma concentration and effect. One of the success stories in 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, Astra Zeneca 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 sales in 2003.[14]

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.[15–17]

Several pharmaceutical companies have successfully obtained patent protection for new methods of use. For example, Merck originally developed, patented, and marketed Finasteride for 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 2 million prescriptions for Strattera were written in its first 9 months in the market.[18–20]

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.[21,22]

Combinations

Does one and one make three? That is the question drug companies are asking themselves these days as they face huge threats to their earnings from patent expirations. One novel solution: combining two or more successful drugs into one tablet and marketing it as a whole new product.

Schering-Plough is looking to extend its giant franchise in its allergy drug Claritin by combining it with Singulair, an asthma drug from Merck. Schering-Plough is not alone. Eli Lilly, Pfizer, and Warner-Lambert are all looking to create new combinations of drugs to bolster earnings and sustain growth. Companies are getting a lot more creative in ways to sustain the product lifespan of drugs. The medical community looks at it as a kind of cookbook medicine. They have an aversion to combination drugs. Nonetheless, it is a strategy that has proved successful for some drug makers[23] [Table 5].

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 lifecycle of Zyprexa and to recoup losses due to the market entry of generic Fluoxetine, Lilly has developed and patented a combination product called Symbyax comprising Olanzapine and Fluoxetine, for the treatment of bipolar disorder. Zyprexa accounted for more than $1 billion in sales in

2003, and the combination product Symbyax is expected to add $100 million in sales to the Zyprexa product line.[24] 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.

Polymorphism Polymorphism has also presented a scientifically challenging issue for biotech companies and a legally challenging one for the courts. Polymorphism is the concept of a molecule assuming multiple crystal structures.[25] Polymorphism can have a 'profound effect on the shelf life, solubility, formulation properties, and processing properties of a drug.'[26] One polymorph of a drug can be more effective than another, easier or more difficult to manufacture, or even dangerous.[27] Polymorphs raise patenting considerations because a company may choose to patent either the molecule's structure, one of its specific crystallized states, or both. Some companies have used polymorphism to their advantage. By patenting a polymorph after the original drug has been patented, a company can extend its period of market exclusivity.[28] However, polymorphism can also present a patenting pitfall. Consider a competitor discovers an unpatented polymorph that is easy to manufacture and is as effective as the original drug. Because it is a polymorph, its production will not infringe on the inventor's patent. Early research to discover a drug's polymorphs and their properties is therefore crucial.

Conclusion

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. Such strategies must be developed before patent expiration and prior to the imminent market entry of generic competitors. At the same time, there should be collaboration between scientists and attorneys. For more efficient creation of patents and subsequent protection of their intellectual 'offspring,' pharmaceutical scientists and patent attorneys need to work closely during the lifecycle of the drug to extend its patent life along with the understanding of the underlying concepts and principles of the others' discipline relating to patents.

Acknowledgments

Authors are thankful to Ms. Aarti Sharma (Jaipur National University, Jaipur, India) for checking the manuscript.

Footnotes

Source of Support: Nil,

Conflict of Interest: None declared.

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Figures and Tables

Table 1

Brand name	Manufacturer	US sale prepatent expiration (in US$ million)	US sale postpatent expiration (in US $ million)	Year expired
Claritin	Schering-Plough	>3	370	2002
Prozac	Eli Lily	>2.9	480	2001
Pepcid	Merck	755	110	2000

Revenue losses following patent expiration and generic drug entry[11–14]

Table 2

Company	Patent expiry year	Brand name	Indications
Glaxo Welcome Inc	2005	Zofram	Nausea and vomiting
	2005	Retrovir	HIV infection
	2006	Imitrex	Migraine
	2008	Serevent	Asthma
	2009	Epivir	HIV infection
Merck and Co	2005	Zocor	Cholesterol reduction
	2006	Proscar	Benign prostatic hypertrophy
	2007	Fosamax	Osteoporosis
	2009	Cozaar	Hypertension
	2013	Primaxin	Infections
		Crixivan	HIV infection
Johnson and Johnson	2006	Risperdai	Psychosis
	2007	Propulsid	Nocturnal heat-burn
Bristol-Myers Squibb Co.	2005	Pravachol	Cholesterol reduction
	2007	Zerit	HIV infection
Pfizer Inc.	2005	Zoloft	Depression
	2005	Zithromax	Infections
	2007	Norvasc	Hypertension
Astra Lab	2009	Trprol-XL	Hypertension
Smithkline Beecham	2005	Paxil	Depression
	2007	Kytril	Nausea and vomiting
	2010	Havrix	Hepatitis A
Eli Lilly and Co.	2011	Zyprexa	Schizophrenia
Zeneca	2005	Zoladex	Breast cancer
Warner Lambert Co.	2008	Rezulin	Non-insulin-dependent diabetes
	2010	Lipitor	Cholesterol reduction
Abbot Laboratories	2008	Depakote	Epilepsy
Novartis	2005	Lamisil	Fungal infection
	2008	Lescol	Cholesterol reduction
Schering Plough Co.	2012	Claritin	Allergies
American Home Products	2006	Prempro	Menopausal symptoms
		Effexor	Depression
Tap Pharma. Inc.	2005	Prevacid	Ulcers

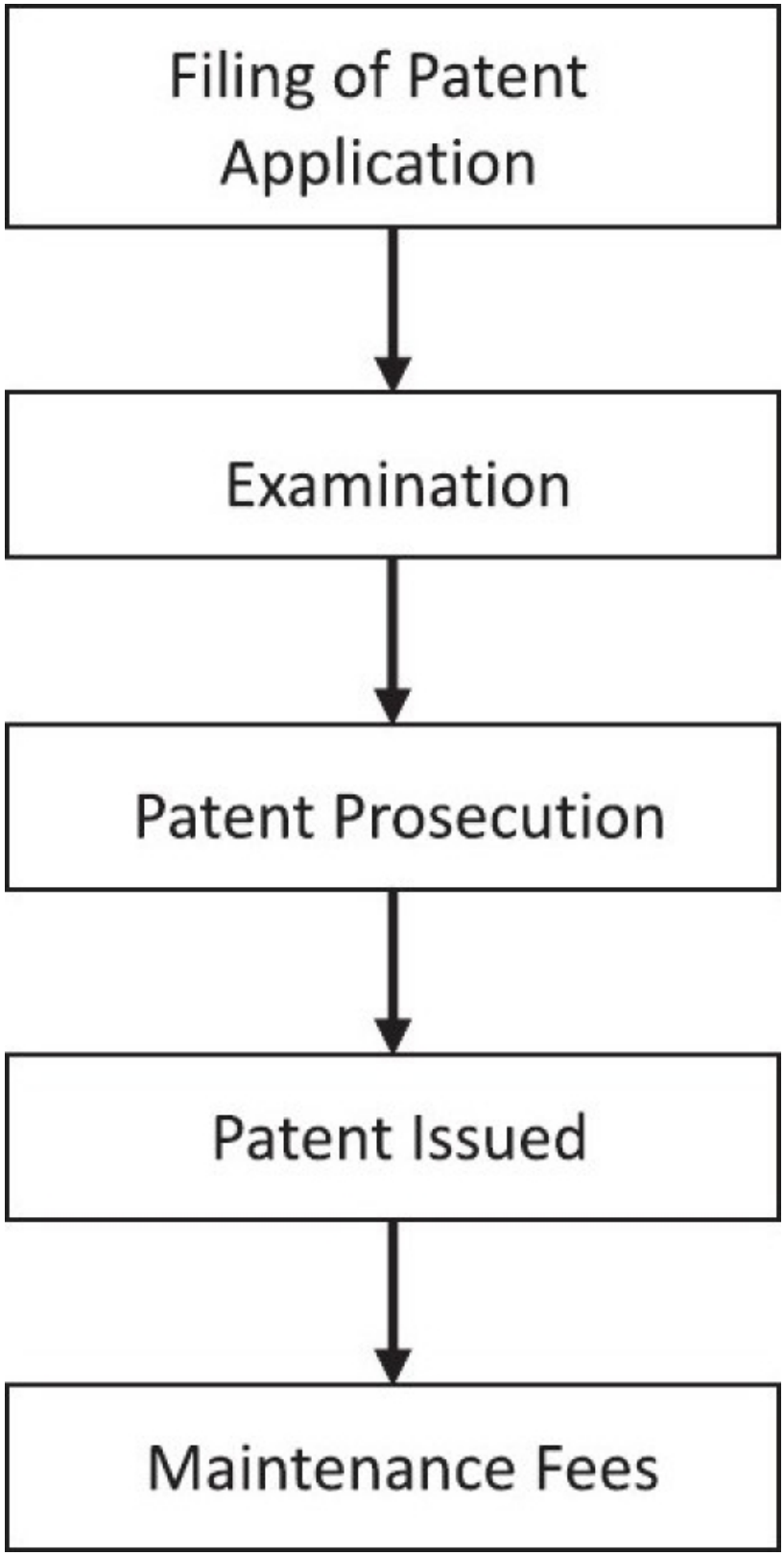
Patent expiry of best selling drugs 2005–2013[16]

Table 3

Brand name	Manufacturer	Revenues in 2002 (US$ billion)	US patents expiration
Zocor	Merck	6.2	2005
Zolosoft	Pofizer	2.9	2005
Ambien	Sanofi	1.5	2006
Paxil	GSK	3.3	2006
Oxycontin	Purdue Pharma	1.5	2006
Pravachol	Bristol-Meyers Squibb	1.5	2006

Blockbuster drugs facing patent expiration[8–10]

Figure 1



U.S. patent application process[15]

Table 4

Drug	Action/indication	Comment
Dexketoprofen	Nonsteroidal ant-iinflammatory drug	Inhibition of cyclooxygenase activity resides in the *S* enantiomer; unlike (*R*)-ibuprofen, (*R*)-ketoprofen undergoes minimal chiral inversion in humans. Reduced dose requirement in comparison to the racemate; formulation as the trometamol salt results in more rapid absorption and onset of action compared to the racemic free acid
(*R*)-salbutamol levalbuterol	β_2-agonist	Use of the racemate is associated with some loss of bronchodilator potency. Studies in humans have indicated that inhalation of (*R*)-salbutamol produces significantly greater bronchodilatation than the equivalent dose of the racemate
Escitalopram	Selective serotonin reuptake inhibitor	*S* enantiomer of citalopram, a potent selective serotonin reuptake inhibitor, which in *in vitro* test systems is between 130- and 160-fold more potent than the *R* enantiomer. Clinical studies in depressed patients have indicated as much improvement with 10 mg daily of the single enantiomer as achieved following 40 mg daily of the racemate, together with a faster onset of action, reduction in side effects, and improved tolerability profile
Levocetirizine	H_1-antihistamine	*R* enantiomer of cetirizine; clinical studies have indicated the equivalence of a 2.5 mg dose of the single enantiomer compared to 5 mg of the racemate, the *S* enantiomer being essentially inactive
Esomeprazole	Proton pump inhibitor	*S* enantiomer of omeprazole; lower first pass metabolism, slower plasma clearance, and increased systemic availability compared to the *R* enantiomer
Levobupivacaine	Local anesthetic	Enantiomers of bupivacaine exhibit stereoselectivity with respect to blockade of sodium and potassium ion channels, the *R* enantiomer being more potent. The cardiotoxicity of the drug appears to be predominantly associated with the *R* enantiomer; *in vitro* investigations have indicated smaller conduction changes following treatment with the *S* enantiomer in comparison with either (*R*)-bupivacaine or the racemate. Clinical studies have indicated that sensory block and the clinical profile following the single enantiomer are essentially the same as the racemate. Thus, the single enantiomer results in a similar clinical profile with a reduction in cardiotoxicity
(*S*)-ketamine	Anesthetic	(*S*)-ketamine has a greater analgesic and anesthetic potency than the *R* enantiomer in both animals and man; postanesthetic emergence reactions (hallucinations and agitation) are predominantly associated with the *R* enantiomer

Racemate to single enantiomer: The chiral switch[23]

Table 5

Company	Drug	Primary use	1999 sales in $
Merck	Zocor	Cholesterol reduction	4.5 billion
Schering-Plough	Ezetimibe	Cholesterol reduction	In development
Merck	Singulair	Asthma	500 million
Schering-Plough	Claritin	Allergies	2.7 billion
Pfizer	Norvasc	Hypertension	3 billion
Warner-Lambert	Lipitor	Cholesterol reduction	3.7 billion
Lilly	Prozac	Depression	2.6 billion
	Zyprexa	Schizophrenia	1.8 billion
Glaxo-Wellcome	Epivir	HIV	527 million
	Retrovir	HIV	139 million
	Ziagen	HIV	140 million

Synergies drug combinations under development