

second edition

The Generic Challenge

**Understanding Patents, FDA &
Pharmaceutical Life-Cycle Management**

Martin A. Voet
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Pharmaceutical Life-Cycle Management
Second Edition

Martin A. Voet, B.S., M.B.A., J.D.

Brown Walker Press
Boca Raton

*The Generic Challenge:
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This book is intended to encourage the innovators to persevere in the face of this adversity and to redouble their efforts to innovate and to continue to see themselves as the valuable contributors to society that they are.

Martin A. Voet
December 3, 2004

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CHAPTER

Putting it All Together: Product Life-Cycle Management

In view of the right of generic companies to copy innovators and obtain approvals of generic drugs in the absence of patent protection after the limited exclusivity periods described in previous chapters have expired, brand name drug owners have developed strategies to protect their long-term investments and current sales. These strategies are known generally as product life-cycle management and are intended to extend the life of innovator products. Professionals involved in strategic marketing also have developed a number of non-product-oriented techniques to enhance a product's success, but the focus of this chapter will be on product life-cycle management by use of patents, regulatory strategies, product improvements and the Hatch Waxman Act.

Generally, life-cycle management (LCM) starts early and ideally is integrated into the entire development cycle itself. That is, even before the product has been developed, the people responsible for development and marketing must have in mind the need to provide an adequate life to the product. LCM involves a number of interactive strategies designed to enhance product life through the primary forms of exclusivity available to pharmaceutical products,

through an interactive mix of patents, product improvements, FDA exclusivity and FDA rulings through Citizen Petitions, all at different stages in the product life cycle.

PATENTS

A product life cycle begins in the initial discovery of a promising lead compound. The first patents are intended to cover the general chemical family or genus of compounds; so patent claims are directed broadly to cover the genus as well as narrowly to cover the lead compound and variations in between. The main emphasis is on the chemical side—identifying chemical structures and methods of manufacturing them.

Development Stage

During the development stage where the pre-clinical, pharmacological and other biological aspects of the lead compound are evaluated, additional patents can be filed on newly discovered medical uses and novel formulations for the drug to enhance efficacy or to overcome drug metabolism or drug delivery issues. Improved methods of manufacture may be developed at that time for scale-up in preparation for clinical trials.

Clinical Stage

During the clinical stage, where the drug is tested in humans, additional patents can be filed on new dosage forms, methods of administration, potential new uses which may come to the attention of clinicians as side effects (which was how Viagra® was discovered) and possible novel drug combinations with other known drugs. Pharmacokinetic data can also reveal patentable aspects of drugs, e.g., a pH change in an ophthalmic solution can unexpectedly enhance drug absorption through the cornea allowing a lower concentration of active drug resulting in

reduced side effects. During this period, additional drug forms also may be identified, such as active metabolites or stereoisomers of the drug having unique characteristics, and polymorphs of the drug such as different crystal structures or hydrates (combinations of the solid drug with water).

Line Extensions, New Uses and Formulations

While the drug is pending approval, there is time to think about line extensions, potential new medical uses, improved formulations for better drug delivery, such as sustained release formulations or once-a-day administration, and improvements in the bulk synthesis of the active drug. Once approved and sold, shortcomings of the drug formulation relating to patient acceptance may come to light that were not apparent from the clinical trials. At this point, an improved formulation may be started to overcome the shortcoming. In addition, work may start on a single isomer improvement or drug combinations with other active drugs.

These techniques typically are applied to innovator drugs, but the same concept applies to a paper NDA drug filing under 505(b)(2) which involves some minor change in the innovator drug or its formulation that may be patentable itself. An example of this is Alcon modifying a patented formulation of an improvement of an innovator ophthalmic drug sold by Merck (Timolol® XE) by using a different gelling agent to get around Merck's patent on its once-a-day drug formulation and at the same time patenting its own new formulation to prevent ANDAs being obtained on its product.

Patent Term Extensions

Finally, any patent term extension that is available for the product should be filed and obtained worldwide. Typical extensions of up to five years are obtainable in the U.S. as well as Europe, Japan, Australia and other countries. The rules in each country

vary, but each country provides formulas to make up for some, but not all of the patent time lost while the drug is going through the required regulatory approval hurdles.

In the U.S. the formula adds a maximum extension of five years to the original patent life, but not longer than 14 years of patent life from date of approval of the drug. The actual term is computed by a formula that applies to the period between IND filing and FDA approval of the NDA. The formula basically provides a day for every day the FDA is working on the file and a half-day for every day the applicant is working on the file. Typical patent term extensions are in the range of two to four years. The Patent Office confirms the dates submitted by the patent holder with the FDA and awards the patent term extension after publication in the Federal Register for complaints by interested parties.

The patent term extension does not actually extend the term of a patent for all of its claims. The patent term is extended only for the approved drug product. The question arises then what *exactly* is the approved drug product?

In an interesting case (*Pfizer v Dr. Reddy, CAFC 2004*), a generic company, Dr. Reddy, took the position against the innovator, Pfizer, that a different ester of an active drug was not covered by the patent term extension and got a Federal District Court to agree. The industry was up in arms over this because such a ruling would make a mockery of the concept of patent term extension if insignificant changes in the approved drug product would not be covered by the patent term extension. In this case, it did not matter which ester was used for the drug, as the active drug moiety was the same regardless which ester was used. The Court of Appeals overruled the lower court, finding that the "approved drug product" meant the active drug moiety and not the exact chemical form of the approved drug.

The result of this case makes it clear that generic companies will not be able to make slight changes in salts or esters or hydrates of an active drug to get around a patent term extension.

In addition improvements by the innovator, which incorporate the same active drug moiety, and which were approved drugs at the time the patent term extension was granted, will be entitled to protection under the original patent term extension and therefore will encourage such improvements.

PRODUCT IMPROVEMENTS

The heart of LCM is product improvements following the launch of an original new chemical entity (NCE). These product improvements enable the innovator to improve the product at minimal cost compared to developing an entirely new NCE, while at the same time dramatically enhancing the future value of the NCE by providing improved medicines to the public thereby extending its useful life.

Active Drug Combinations

Suitable improvements fall into a number of well-known categories including new excipients that may be used alone or in combination with new dosage forms or concentrations of the NCE to reduce side effects and/or to enhance patient comfort or compliance. Line extensions, such as combinations of different active drugs, for example, in the ophthalmic industry, where drugs are used in combination such as topical steroids combined with antibiotics to treat infection and inflammation.

An example of combining two known drugs for patient benefit is Vytorin, a combination approved by FDA in 2004. Vytorin is a combination of two well-known cholesterol-lowering drugs: Merck's Zocor® and Schering-Plough's Zetia. The patent for Zocor expired in 2006 so the combination with the longer patent life of Zetia made good business sense as well as medical sense, since Zetia limits absorption of cholesterol in the digestive tract while Zocor, a statin, limits cholesterol production in the liver. The combination reduces

cholesterol about an extra 20%. Since that combination proved successful, the two companies have announced they are planning another combination of Zetia with Lipitor after the patent for Lipitor expires in 2010 or 2011.

Single Isomers

If the original drug was a racemate (an NCE consisting of two optical isomers – think of it as equal amounts of a left-handed and a right-handed version of the same chemical compound), a typical improvement is use of one of the isomers alone that sometimes has better biological activity or lesser or fewer side effects relative to the other isomer and the racemate. An example of this is the prescription successor to Prilosec®, named Nexium®, and promoted as the “Purple Pill®”, by Astra Zeneca. However, this strategy is no longer at the top of the LCM list for a number of reasons.

One potential problem with developing single isomers from known racemates is their potential for limited exclusivity. The FDA considers them new formulations rather than new chemical entities (NCEs) so that the FDA exclusivity is only three years rather than the five years for an NCE. In addition recent cases have held some stereoisomer patents invalid on the grounds of obviousness. For example, the European patent for Nexium was recently invalidated, as was the U.S. patent for Altrace. However, the U.S. patent for Lexapro was recently upheld. As the law now stands, if the stereoisomer has unexpected properties not found in the racemate and/or if it is not obvious how to separate the stereoisomer from the racemate, the stereoisomer may be patentable.

New Delivery Systems

New delivery systems, such as transdermal patches instead of oral delivery, and controlled release formulations for oral delivery,

provide once-a-day dosing versus multiple-times-a-day dosing. Patients find this more convenient and doctors prefer it for improved patient compliance, i.e., the patient will more likely take the proper dose of the drug.

Each of the foregoing product improvements is entitled to a three-year FDA exclusivity if clinical trials were required for FDA approval, and of course it is likely that the new formulation, drug entity or delivery system may be patentable. If the improvement provides valuable new benefits, doctors will prescribe the new formulation instead of the old one, and so a generic company will not be able to make much headway in trying to sell the older, less convenient or more difficult-to-use version of the drug. Even without a patent, the additional three-year exclusivity would extend the life of a product significantly, since typical product life is only about 12-14 years even if the product is patented. (Recall one cannot even get a patent term extension if there is more than 14 years of life remaining on a patent.)

Orange Book Listing of Improvement

There is a further interactive effect with FDA and patents on improvements. If the innovator gets a patent on the improvement, the patent must be listed in the Orange Book. If a generic company wants to copy the improvement after the three-year exclusivity, it must file another ANDA and another Paragraph IV certification and the innovator can sue again under the Hatch Waxman Act and the FDA is prevented from granting an ANDA on the improvement for another 30 months.

Original Product Replacement

Another strategy is to launch the improvement early enough so that the innovator can inform patients and doctors about the improvement and if doctors and patients switch to the improvement, the original product may lose much of its market before

a generic drug is approved. When the generic drug is approved, there is essentially no market for it since all the patients are using the improvement instead. In some cases, e.g., if the improvement relates to improved safety, the original product can be withdrawn from the market making it even more difficult for the generic drug to get market share.

OVER-THE-COUNTER STRATEGY

Another strategy is to develop and launch an over-the-counter (OTC) version of the drug just prior to the time the original product's patent life expires, as done by Schering-Plough with Claritin® and Astra Zeneca with Prilosec®. This transfers a significant portion of the old prescription market to the new OTC market for the innovator and reduces market size for the generic company.

FDA CITIZEN'S PETITIONS

If there is a concern that the generic drug may be different in such a way that safety or effectiveness is called into question, another avenue is to make objections to the suitability of the generic product with the FDA by filing a Citizen's Petition (CP). These are formal written requests to the FDA that the FDA is obliged to consider and reply to publicly. For example, Wyeth filed a CP on the suitability of an ANDA for its conjugated estrogen, Premarin®. After lengthy deliberations, the FDA agreed with Wyeth and would not approve an ANDA for Premarin, based on its unique formulation that the company said could not be duplicated by a generic product. (Premarin is extracted from the urine of pregnant mares and is a natural hormone complex more like a biological and not readily duplicated chemically.)

In response to complaints by the generic industry that Citizen's Petitions were being filed by branded drug companies for the purpose of delaying approval of ANDAs, Federal legislation was passed

in late 2007 providing that FDA may not delay the approval of a pending ANDA or 505(b)(2) application as a result of a CP unless the FDA determines that the delay is necessary to protect public health. In addition, the FDA is authorized to deny any CP if it was submitted for the primary purpose of delaying approval of the ANDA if the CP does not raise valid scientific or regulatory issues. Finally the FDA must take action on the CP within 180 days from its submission. There is also language to prevent a CP from causing the loss of any part of the 180-day first-filer exclusivity from approval delays caused by a CP.

AUTHORIZED GENERICS

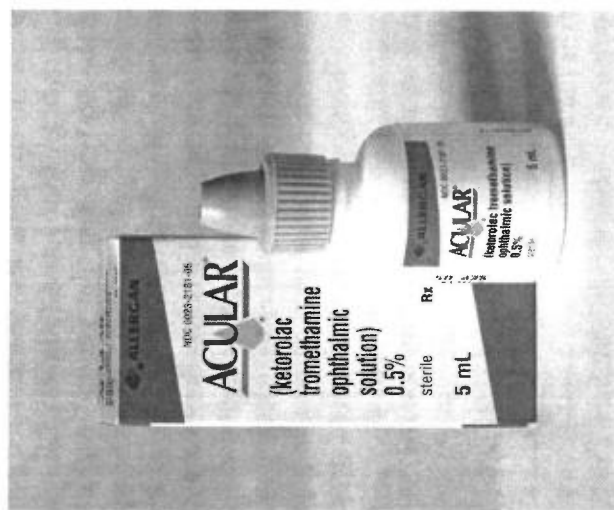
In an interesting turnabout, two major generic companies, Mylan Pharmaceuticals and Teva, filed CPs with the FDA to ban so-called "authorized generics". Authorized generics are generic products that an innovator company licenses to a third party during the 180-day first-filer generic exclusivity period, thereby effectively taking away the exclusivity period from the generic company that had it. The generic industry counts on the 180-day exclusivity period to make large profits and it is a key growth driver. The presence of a second generic product with lower prices effectively reduces their earnings and has the potential to dramatically alter the current innovator/generic equilibrium. Though it is clear authorized generics benefit consumers with lower prices for drugs, the generic industry has been aggressive in trying to prevent them as they reduce generic company profits.

In June, 2004, the FDA denied the CPs and confirmed the rights of the innovator companies to sell authorized generic products indicating that the price reductions in the cost of generic drugs it provided was appropriate and in the public interest. Examples of recent authorized generics include the well-known antidepressant Paxil® (license granted to Par Pharmaceuticals by GlaxoSmithKline) and

the oral contraceptive Ortho-Tricyclen® (licensed by J&J to Watson Pharmaceuticals) though Barr Laboratories had first-filer exclusivity rights.

Since the FDA ruling, the launch of authorized generics has become commonplace. Subsequent litigation on the issue resulted in authorized generics being upheld by the courts. As a result, we are seeing more deals between innovators and certain generic companies for authorized generics. Turned away by the FDA and the Courts, the generic industry is now trying the political route. Several bills were pending in 2007 to ban authorized generics, but none have passed as of the end of 2007.

EXAMPLES OF LIFE-CYCLE MANAGEMENT



8. Acular 0.5%

An innovative drug product, Toradol® (ketorolac tromethamine), a non-steroidal anti-inflammatory drug (NSAID), was invented by Syntex (now part of Roche) in the early 1970s and was approved by FDA for systemic treatment of serious pain conditions. It is non-narcotic and non-habit forming and does not cause physical or mental dependence, as narcotics can. It is administered orally or by injection. Syntex filed and obtained patents on the new chemical entity, for its use in treatment of serious pain and on its method of manufacture.

Additional research, begun in the late 1970s, led to the discovery that the compound could also be used topically in the treatment of certain eye conditions. A new patent was therefore filed for treatment of conditions of the eye with topical formulations



9. Acular LS 0.4%

containing ketorolac tromethamine. Syntex researchers then tried to formulate the compound into a commercially acceptable eye-drop and ran into problems obtaining a robust, stable formulation. A number of Syntex formulation scientists worked for several years on the problem and eventually solved it through the use of a special stabilizer that had not previously been used for stabilizing ophthalmic pharmaceutical products. An additional patent was obtained on the ophthalmic formulation containing the new formulation with the new ophthalmic stabilizer.

The eye drop product was approved by FDA as Acular 0.5% and launched in 1992 and three patents were listed in the FDA Orange Book. The original 1995 patent expiration date of the compound patent was extended to 1997 by patent term extension. The expiration date for the ophthalmic use patent was 2002 and the expiration date of the formulation patent was 2009. Since the NCE patent had been extended, no further extensions could be made to the improvement patents. In addition, the FDA requested that a pediatric study be done and after its completion, the patent dates were effectively extended by six months. The new ophthalmic formulation was entitled to a three-year FDA exclusivity for its new indication/new formulation for relief of ocular itching due to seasonal allergic conjunctivitis. After further clinical studies during the 1990s, the product was also approved in 1998 for an orphan condition, namely, inflammation following cataract surgery. This entitled the innovator to a seven-year FDA exclusivity to 2005, but only for that indication.

The Canadian based generic company Apotex filed an ANDA for Acular 0.5% in 2001 (for the first approved indication only since the second indication was still protected by orphan designation) and sent a Paragraph IV certification asserting the formulation patent was invalid and not infringed. Within the 45-day period provided, a patent infringement suit was filed against Apotex and litigation commenced in the Federal District Court in San Francisco as a bench trial before U.S. District Court Judge Martin Jenkins, without a jury. Under the terms of the Hatch

Waxman Act, the FDA was not able to approve the ANDA for the product for up to 30 months from the date of notice of the Paragraph IV certification or until there was a Court decision concerning the patent.

The original 0.5% product tended to cause transient burning and stinging in the eye when it was used. To improve the product, the company began developing a new formulation that used a lower concentration of the active drug, with the same effectiveness, and which was designed to be more comfortable to the patient. Patients testing the improved 0.4% reformulation reported no burning and stinging on installation of drops. In addition, the improved product was tested and approved for a new use, namely, reduction of ocular pain and burning and stinging following LASIK corneal surgery. The improvement was approved by FDA as Acular LS and the new product was launched in 2003.

Thereafter, Acular LS was listed in the Orange Book under the same formulation patent as the original product and received a three-year new use exclusivity based on the newly approved medical use. A short time thereafter, Apotex copied the improvement, filed an ANDA for it and sent a Paragraph IV notice. Apotex was sued within the 45-day period provided, and Acular LS likewise was litigated in the same court as the first product.

The multi-week trial on Acular 0.5% was completed by the summer of 2003 before the end of the 30-month period; however, the Court had not issued its ruling by the end of the 30-month period in October, 2003. On request of the company, the Court extended the 30-month period until the end of 2003, or until it issued its ruling, whichever came first.

The District Court ruled in December, 2003 that the formulation patent was valid and infringed (*Syntex and Allergan v Apotex*, 2003). Apotex subsequently appealed to the CAFC. The CAFC concluded in 2005 that the District Court had gotten it mostly right, but they remanded for issues having to do with the Court's fact findings on obviousness. In 2006, the District Court

reconsidered its ruling in light of the views of the CAFC and concluded its original decision was the correct one. The CAFC affirmed that decision in 2007. Thereafter Apotex unsuccessfully requested the decision be reviewed by the Supreme Court. The case now being final, the FDA was instructed by the Court in accordance with the provisions of the Hatch Waxman Act not to approve the Apotex ANDA until expiration of the final patent listed in the Orange Book. In addition, the FDA will not approve the ANDA until the expiration of the pediatric extension six months after patent expiration in late 2009.

The trial on Acular LS was handled by the same Court in 2007 by summary judgment again upholding the patent just before the end of the second 30-month period. Apotex also appealed that decision to the CAFC and it will be 2008 until the final answer is received on the improvement.

This example shows how the combination of good patent protection on each new invention (compound, second medical use and formulation), coupled with use of the Orange Book listing, patent term extension, an improvement to the product and four different FDA exclusivities (new use, new formulation, orphan and pediatric), have provided a reasonable life to the innovative eye care product and provided the public with new, innovative medicines for treatment of three important eye conditions. Note that the compound and ophthalmic use patents were never challenged. If there are no further generic challenges, the novel eye care product family that was originally launched in 1992 will have a life of about 17 years, after which it likely will become generic in late 2009.

Hypothetical Example 2- Lack of Initial Patent Protection

A hypothetical example of the application of life-cycle management is a drug with substantial sales, but little or no patent protection. This can happen for a variety of reasons. Here is one example.

The active drug compound is discovered and patented in the usual way by the innovator; however, the compound is unsuccessful for its original indication and is set aside by the innovator, as often happens in pharmaceutical drug research, and information concerning it is published. Some years later, compounds like it are found to be useful in a related indication and the owner licenses the compound to another company interested in the related area. Unfortunately, the prior publication of the information on the compound also mentioned the possibility of using the compound for the related condition, so it is too late to file a patent covering the new use since the publication is prior art and bars a patent on the related condition.

Notwithstanding the lack of patent protection, the licensee decides to go ahead with the development of the compound for the new use and is ultimately successful in obtaining FDA approval, but somewhat later than expected and by that time, the compound patent has expired. The approved product is entitled to a five-year FDA exclusivity period as it is the first approval of the active drug compound for any medical use. However, the compound patent cannot be listed in the Orange Book because it has expired. As a result, the product is likely to have a short life since the law allows a generic company to file an ANDA at the end of the five-year exclusivity, which may not provide sufficient time for the second company to absorb its development costs as well as the royalty due to the licensor for the license to the IND and the pre-clinical and early clinical work done by the original innovator.

If the remaining patent life is less than six years, one is actually better off without a patent since the presence of a patent listed in the Orange Book allows an ANDA to be filed four years after approval. If no patent is listed, the ANDA cannot be filed until five years after approval (or five and one-half years after approval if a pediatric extension is obtained). Since the FDA can't accept the ANDA until the end of the five years (or five and one-half years with the pediatric extension), the patent having a shorter term

than that of no value and in fact has a negative value as it allows the ANDA to be filed a year earlier.

Once the FDA approval parties are over, the company's strategic marketing people start getting worried. They can see that the product life will be too short and they start to think how that can be remedied. They call in consultants and discuss the matter with in-house scientific, regulatory and legal staff and start to develop a plan to improve the product with the hopes of also improving its limited life.

The first improvement selected is to do a clinical trial in children that will allow the company to provide the drug product to children and also obtain a six-month pediatric extension giving the product five and one-half years instead of five years of exclusivity.

The second improvement decided upon is to improve patient acceptability. The current drug must be taken twice daily. Patients are not overly pleased with this regimen and doctors are unhappy because patients sometimes forget to take the medication and as a result compliance is not good. The company decides that a suitable improvement would be a once-a-day sustained release product that would provide better patient acceptance and better compliance.

A third improvement suggested involves a new combination of the old drug with a new active drug in the new once-a-day formulation which provides a new treatment paradigm for patients.

Work is started immediately on the first two improvements and the formulators come up with a novel and unique sustained release once-a-day formulation that is put in the clinic for testing. Five years after the original product is launched, the new product is approved by the FDA following successful clinical trials and a new NDA filing. Several patent applications are filed on the new sustained release formulation, including the novel aspects of the formulation itself, as well as new dosing levels resulting from the use of the new formulation based on the discovery that the new dosing levels improve efficacy and reduce side effects.

The new once-a-day sustained release product is launched and immediately receives rave reviews from patients and doctors alike. Within a year, over 90% of combined product sales are the sustained release form. As a result, the company decides to withdraw the original product, as scant sales no longer justify the costs of continuing its manufacture. In addition, the new product receives the three-year FDA exclusivity for a new formulation.

By this time, the pediatric study on the original product is completed and the original product is awarded a six-months pediatric extension. Since the improved product was approved at the time the pediatric exclusivity was awarded, it applies to both products. Work on the third improvement, the combination product, is now also underway.

A year earlier, the first patents on the new sustained release formulation are granted and listed in the Orange Book. These patents are listed under the new product only as they do not cover the original product. As a result, an ANDA for the old product still cannot be filed until the end of the five and one-half year exclusivity period for the original product. Even though patents have been listed in the Orange Book, an ANDA may not be filed for the *improvement* prior to five and one-half years from the date of the original product approval, and the ANDA may not be approved by FDA until the end of the three-year exclusivity period for the improvement. The pediatric exclusivity also applies to the new patents and they are shown as extended in the Orange Book.

Several generic companies have been preparing ANDA submissions for the original product and file them at the end of the five and one-half year exclusivity period. They are approved within 18 months (seven years after the original product approval) and are launched. There is no first-filer 180-day exclusivity, since there was no Paragraph IV certification because there were no patents listed in the Orange Book for the original product.

The market for the improved sustained release product is not affected very much by the availability of the cheaper generics for the original product, as both patients and doctors prefer the improved product. However, it is now available as a lower-cost generic drug for those persons or institutions for which lower-cost medicines are deemed of greater importance than the benefits of the improved product.

The generic companies are not very happy with the resulting sales however, so they decide to copy the improved sustained release product. After review of the patents filed in the Orange Book, the generic companies conclude that the patents have sufficient flaws that they could be overturned in court so they copy the improved product and do the work necessary to file new ANDAs on the improvement product. They are filed about 18 months later during the three-year exclusivity period, which is allowed.

After filing, the generic companies provide a Paragraph IV certification to the innovator and the innovator files a patent infringement suit within the statutory 45 days. The filing of the suit automatically prohibits the FDA from approving the new ANDAs for 30 months or until there is a Court decision. In addition, the generic company who is the first filer to challenge the patents is entitled to the 180-day exclusivity if its ANDA is approved. Interestingly, the filing dates of the ANDAs are kept confidential by the FDA, so it is difficult for anyone to find out which company will get the 180-day exclusivity before the first ANDA is approved. Within 18 months of filing, the FDA provides *tentative* approval to the ANDAs for the once-a-day formulation. Tentative approval means that the ANDAs are approved subject to resolution of the patent issues. If the patent is held invalid or not infringed, the tentative approval is converted to final approval immediately. If the patent is held valid and infringed, the ANDAs will not receive final approval until the patent and any exclusivities expire.

By this time, the combination product has been through clinical testing and the results of the clinical trials have shown certain unexpected patient benefits and these benefits are noted and patents are filed on the new combination based on these unexpected results. The new combination is approved and launched and when the patents for the new combination are granted, they will be listed in the Orange Book. The new combination also gets a three-year new formulation exclusivity. The new combination product and its patents act as a back-up in the event the once-a-day patents are held invalid. In this manner, the innovative company tries to stay at least one step ahead of the generic companies by constant improvements.

If the generic companies are not successful in overcoming the patents on the once-a-day product, the Court will rule that the FDA may not approve their ANDAs until the patents and any pediatric exclusivity expire. If the generic companies succeed in overturning the patents, the FDA will be able to approve the ANDAs at any time after an adverse decision of the District Court. However, even if the innovator loses the case in the District Court, a generic company may choose not to launch its copy until the case has been affirmed on appeal, which ordinarily takes about 12 months. This is because the generic company could be liable for lost profits of the innovator if it launched the generic product and then later the case was reversed on appeal and the patents upheld. In addition, the 180-day exclusivity period does not start until a final ruling of the Court of Appeals, so the first-filer generic company can afford to wait until the outcome of the appeal.

To do the math, the innovator receives five years exclusivity for the original product, plus six months pediatric exclusivity, plus three years exclusivity for the new sustained release formulation, plus another six months pediatric exclusivity, plus 45 days and 30 months for the Paragraph IV certification, plus 12 months for the appeal. This adds up to about 10-11 years—almost double the life cycle over the original product life. In

addition, the combination product, if attempted to be copied, also receives similar added life. The net result of the foregoing is the innovator has significantly added to the useful life of its drug product *franchise* while providing value and convenience to patients. Of course, if the patents are upheld, the improvement product's life will continue until the patents expire or until a better drug product comes along.

These examples illustrate the interactive, multi-faceted nature of life-cycle management integrating patents, FDA exclusivity and product improvements. A good life-cycle management program uses all three in parallel for effectiveness and for redundancy, so that failure of any one, e.g., loss of patent protection on the original product, will not necessarily result in a short product franchise life.

Biotech companies must now also be cognizant of LCM as the sun is setting on the golden age of branded biologicals. Goldman Sachs analysts have estimated that the generic biologicals market will be nearly \$12 billion worldwide in 2010. Large generic companies such as Teva, Sandoz and Barr Labs are currently focusing on the development of these types of products. This suggests biotech companies also will have to start thinking about LCM if they are to maintain their innovative edge in the future.

8 CHAPTER

Conclusions and Final Thoughts

Congratulations. All of you are now experts in pharmaceutical product life-cycle management, or certainly compared to the average professional, wellinformed on the subject. While I have tried to keep the explanation of the subject light and hopefully interesting, it is a serious matter which affects the lives of millions for better or worse. Some basic matters need to be considered:

- Innovative pharmaceutical companies must be encouraged to continue to innovate.
- Countries need to have an industrial policy as well as a drug policy to foster innovation.
- The generics industry must be allowed to offer low-cost medicines to people who need them.
- The laws need to maintain the delicate balance between fostering new innovative drugs and providing good quality, inexpensive generic drugs.