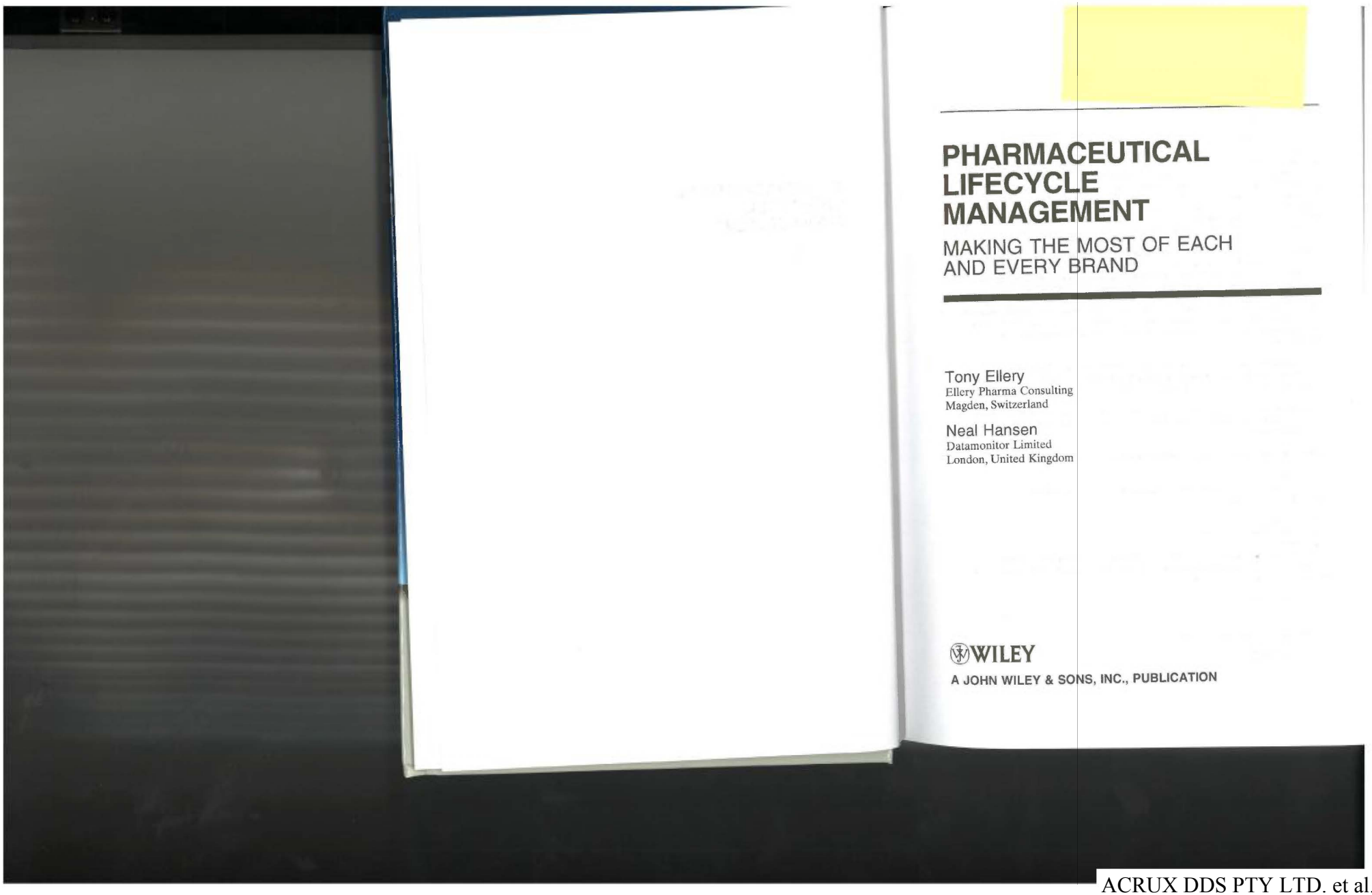

PHARMACEUTICAL LIFECYCLE MANAGEMENT

MAKING THE MOST OF EACH AND EVERY BRAND

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This book is dedicated to
Judith, Glyn, Simon, and David Ellery
and to Nicky, Bethany, and Alex Hansen.

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CHAPTER 3

The Life Cycle of a Pharmaceutical Brand

As we have seen, the characteristics of product life cycles vary considerably between industries. Let us now concentrate on the class of product that is the subject of this book, the branded prescription pharmaceutical.

There are a number of specific features of the pharmaceutical industry that strongly influence product life cycles, and it is essential that these are fully understood if one is going to be successful in designing lifecycle management (LCM) strategies.

Four of the important special features of the pharmaceutical industry that influence LCM are the following:

1. *Drugs Are Easy to Make.* Most drugs are rather cheap and easy to manufacture, so the entry barriers as far as manufacturing is concerned are low. Furthermore, the cost of goods sold (COGS) of high-priced branded drugs represents a relatively low percentage of sales. Dozens if not hundreds of companies are perfectly capable of making exactly the same drug as is contained in the vast majority of branded products. This is particularly true of small molecules and somewhat less true of large biological molecules, as we shall see later. In most cases, however, a brand company cannot rely on competitors not being able to manufacture the same molecule, to the same quality standards. Contrast this with another industry with high development costs, aircraft manufacture; Boeing does not have to worry that dozens of other companies will copy the Dreamliner!

   Not only is it easy to copy a drug, but the capital investment needed to set up labs and manufacturing facilities capable of developing the copy product and then producing it in large quantities is not very high. The innovator has to spend heavily to prove that a new molecule is safe and effective, but these investments do not have to be repeated by the

Pharmaceutical Lifecycle Management: Making the Most of Each and Every Brand, First Edition. Tony Ellery and Neal Hansen.

developers of copy products, as they are using the same molecule and can rely on referring to the data of the originator to gain regulatory approval, just as long as the copy product behaves in the same way in the body, that is, is bioequivalent. This is, of course, the basis for the generic drugs industry, and as we shall see later, it was the concept of bioequivalence in the Hatch–Waxman legislation in 1984 that allowed the generics industry to take off in the United States.

2. *Patents Prevent Copy Products.* Key to the very existence of the branded pharmaceutical industry is therefore the ability to patent a new molecule and thus obtain the exclusive rights to sell it. Only so can the brand company demand prices that are high enough to recover the high costs of developing the molecule. We will be looking at patents in considerable detail later in the book. From the point of time at which a new molecule is first discovered, the innovator company can expect about 20 years of protection during which time no other company is allowed to commercialize the same molecule, and such a patent is valid in most countries of the world.

3. *Consumers Do Not Pay for Drugs.* Branding in the consumer goods industry is very different from branding drugs. Consumer-goods advertising seeks to create an image of the brand in the eyes of the consumers which convinces them to pay a much higher price for the product than they would be willing to pay if that image was absent. This concept is called "value creation"; simply put, it convinces a consumer to accept a price higher than could be justified by the costs of raw materials plus manufacturing and distribution, and more than could be justified by an objective, nonemotional comparison of the value of the brand compared to alternative, cheaper product offerings. In some cases, the added value created is in the brand name of the company, in other cases, it is in the individual products. As an example of branding at the company level, customers will pay high prices for a Mercedes-Benz automobile, and the individual model descriptions (CLK, G550, etc.) are of secondary value; consumers would not pay premium prices for a Dodge G550. A good example of branding at the individual product level would be products like Lipton, Flora, Omo, Vaseline, and Lifebuoy. They are all made by Unilever, but how many consumers are aware of that? If Unilever changed the Lipton brand name to "Smith Teas" tomorrow, their sales would plunge as the value is in the individual brand name. Indeed, when Kellogg's decided to rebrand its kids breakfast cereal Coco Pops to Choco Krispies in the United Kingdom, to bring the brand name in line with the United States, Germany, and Spain, sales plummeted. In the end, the Coco Pops brand was restored after research suggested 92% of consumers wanted the old brand back.

   There is much less value in a brand name in the prescription pharmaceutical industry for the simple reason that the consumer, the end user

of the drug, is in many cases not the person making the buying decision. Until comparatively recently, the physician made the buying decision; he decided what to write on the prescription, and the pharmacist had to dispense it as written. It is reasonable to suppose that physicians, with their scientific education, made their choices based mainly upon the extensive controlled scientific data generated for the different drugs, as well as upon their own experiences with the alternative therapies. Of course their choices were influenced by advertising and detailing by pharmaceutical sales forces, and by consumers exposed to direct-to-consumer advertising requesting specific products, but the objective, data-driven component of their choices was likely to be much more than, say, a housewife choosing between Omo and Persil, or a smoker choosing between Marlboro and Camel cigarettes. But the prescribing decision was certainly not driven by price—indeed in most cases, the prescribing physician did not even know what the price was! However, in recent years, in many countries, the individual physician is no longer the decision maker. Medical insurances determine which drugs will be reimbursed and which will not, and this limits the physician's choices; once the patent on the drug has expired, the various government measures that we have already considered activate, and the patient is likely to receive a generic rather than the brand. The medical insurers are not interested in the brand name, at either the company or individual product level. They are only interested in choosing the cheapest drug available—or the cheapest available version of the same drug—unless there is solid, numerical evidence that an alternative brings enough additional benefit to justify any price premium. In the case of generics, the price premium of the original brand is huge and a bioequivalent represents a much better deal for the payer. Third-party payers are very unresponsive to advertising, and there is effectively no emotional component of their decisions.

In self-pay markets like India and South America, pharmaceutical branding is more effective, because the patient can decide whether to pay the incrementally higher price for their preferred brand, or for the brand over the generic, and then the emotional factors come into play just as they do with other categories of consumer goods. There is a moral issue here, of course, as paradoxically, the more expensive original drugs thus tend to retain a higher market share than the cheaper generics in precisely those poor countries which can least afford it. This is compensated for to some extent by the fact that the price differential of the brand to the generics tends to be smaller in such countries.

As we shall see later, one option for a brand which will soon be facing generic competition in countries where prescription drugs are paid for by insurers rather than the consumer may be to move the brand to nonprescription, self-pay status ("over-the-counter" [OTC] drugs), thus again directly addressing the emotional preferences of the consumer. Not

all OTC switches are commercially successful, and of course, many categories of drug cannot be obtained without a physician's prescription. Nevertheless, there have been several examples of very profitable OTC switches, including Zantac®, Advil®, Claritin®, and Prilosec®.

4. *Governments Set Prices and Support Generics.* We have already considered this in the previous chapter, and will be looking at it in much greater depth later in the book. Suffice it to say here that in most developed markets, the prices that a branded pharmaceutical company can ask for a patented new drug are not determined solely by competition and by market forces, but by government policy. After patent expiry, governments provide many different kinds of incentives for physicians to prescribe generics, pharmacists to dispense them, and patients to use them.

3.1 LIFECYCLE CURVE OF PHARMACEUTICALS

These, then, are four features of the branded pharmaceutical industry that determine how the lifecycle curve will appear for a patent-protected drug. The curve varies considerably from case to case, the indication for which the drug is used and the geography under consideration being the main two determinants. The curve shown in Figure 3.1 is fairly typical for a mass-market drug (family practitioner-prescribed) in the United States.

Let us compare this with Figure 2.2, the curve for a typical industrial product, to see where the main differences are and what causes them.

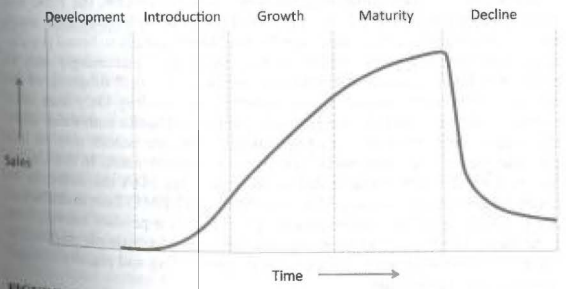

FIGURE 3.1. Lifecycle curve of a mass-market drug in the United States. *Source:* Ellery Pharma Consulting.

Often these drugs target multiple smaller indications, which are introduced successively over the life of the drug. Novartis's Gleevec® would be a good example. Initially launched to treat chronic myeloid leukemia (CML) in 2001, by 2006 Gleevec was also approved for the treatment of a whole portfolio of other orphan indications. All were small, but added together they meant annual global Gleevec sales of over US$3 billion. Gleevec is included in this book as one of our case histories. As another example, biologics developed to treat autoimmune diseases may be tested first in psoriasis patients, where clinical trials are cheaper and faster to complete than, for example, in the bigger and potentially more profitable indication of rheumatoid arthritis.

3.1.2 Lack of a True Maturity Phase

With many drugs there is often no true Maturity Phase, no real plateauing of sales, as sales continue to grow right up to the moment when a sudden decline sets in. The reason for this is that branded drugs are frequently still in their Growth Phase when this is "artificially" cut short by patent expiry, successful challenge to the patent or "at-risk" launch by generic companies, and the subsequent appearance of multiple low-priced generics on the market. Increasingly, it is not even necessary that the patent on the brand itself expires to trigger the start of the Decline Phase. Because of the multitude of me-too drugs on the market, as soon as the basic patent expires on the first brand in a drug class, generic pressure is exerted on all the patented brands in that class too. This relatively new phenomenon of therapeutic substitution was first seen with the statins in Germany, and it is starting to reduce the attraction to companies of developing late-entry "me-too" compounds.

3.1.3 Precipitous Decline Phase

The loss of sales as the Decline Phase is entered is precipitous in many markets and has been likened to falling off a cliff. At patent expiry (or in the United States in the special situation of expiry of 180-day exclusivity, which we shall consider later), cheap generics flood the market. Because the entry barriers after patent expiry are low, because third-party payers do not have brand loyalty, and because government incentives promote the use of generics, brand sales are quickly lost. Usually, it is not a viable strategy for the brand company to attempt to match the generic prices, as margins are so low. Instead, the originator is likely to stay with the high price—or even try to increase it—and continue to sell to the small, non-price-sensitive "laggards" who are suspicious of generic drugs.

While sales decline rates are generally steep and getting steeper in the United States, Europe, and Japan, different factors do determine the rate of sales decline.

3.1.1 Slow Rate of Growth during the Growth Phase

Growth tends to be slower for drugs than for many other industrial products. Why should this be?

Physicians are understandably reluctant to move patients to a new drug until it has proven its worth. Buying the newest cell phone obviously involves a lower risk than moving a sick patient from a therapy that is controlling the disease to one that might or might not prove to be better, but which might have side effects. Understandably and justifiably, the growth curve will be steeper in the case of a new therapy for a hitherto untreatable or uncontrollable disease and slower for a me-too drug or for a new drug class where established drug classes are already performing well.

Added to this, drug companies are severely limited regarding how much they can promote a new drug until it has been approved, so the kind of premarketing that is performed with a new Hollywood film or a new model of automobile is not possible with a new drug. There are a limited number of ways that brand companies can legally premarket their new brands. For example, large clinical trials are necessary to get health authority approval for a new drug, and selecting clinical centers for the trials in the major target markets, and utilizing physicians who are opinion leaders ("early adopters") in these markets, will increase awareness of the new brand even before it can be sold and promoted. And careful selection of the patient population to be treated, the parameters chosen to demonstrate efficacy and safety, and the comparator drugs selected for use in the trial all serve to position the new drug in the minds of its future prescribers and payers. The Internet facilitates the rapid spread of information about drugs that are in development even before approval, so that patients will also have a much higher awareness of new drug introductions than was the case in the past.

Lately, and especially following the withdrawal of Vioxx®, the Food and Drug Administration (FDA) and other health authorities have become much more cautious about letting new drugs be introduced initially to broad populations. This means that the rollout of the new drug is increasingly only in patients with special need of it, which is often a rather small subgroup of the broader patient population that may ultimately use the drug. Only later, once an extensive safety database has been established, will health authorities allow the drug to be used in broader populations where the benefit may be less pronounced and the risk–benefit ratio therefore less favorable. In the United States, the FDA Amendments Act of 2007 gave the FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks. These REMS programs can vary in their severity from simple medication guides and communication strategies to full monitoring and registry systems to ensure appropriate use.

An additional factor contributing to the relatively slow initial growth is that more and more biologics are being developed in place of small molecules.

3.2 FACTORS AFFECTING RATE OF CONVERSION TO GENERICS

3.2.1 Government Policy

As we have seen earlier, some governments are more aggressive about promoting generics than others, and this fact leads to different rates of generic substitution after patent expiry. The United States remains to this day the most aggressive generic market, with generics often taking 95% of volume share within the first 12 months. One remark is necessary regarding any observed generic erosion figures for the United States, which are often an average of two very different situations. In the United States, it is possible for one generic company to get 180 days co-exclusivity with the originator following patent expiry. This generic company maintains a high price, so that sales erosion of the brand is much slower. We will be looking at the whole issue of 180-day exclusivities later in the book. Where this effect is not present, generic erosion in the United States is faster than in any other major market. For example, sales of Novartis's antifungal treatment Lamisil® in the United States were eroded by 93% within 6 months of patent expiry and the entry of generics in July 2007, following the simultaneous launch of 14 generics upon patent expiry.

Outside the United States, generic erosion rates can vary significantly between countries. In Northern European markets, such as Germany, the United Kingdom, and Scandinavia, generic erosion rates are high, with specific policies such as pharmacist substitution and generic prescribing and dispensing targets all used aggressively to drive generic uptake. In these markets, erosion rates of greater than 50% after 12–18 months can be expected, with some drugs seeing much greater erosion. By contrast, in many of the Southern European markets, generic erosion rates are much lower, with Spain and Italy often seeing generic erosion rates of less than 20% after 12–18 months. In these markets, reference pricing policies that often see the branded companies reducing their prices to stay within a reimbursement bracket lead to cost savings without extensive generic penetration. In general, individual country dynamics play a huge part in the impact of patent expiry and the speed and depth of generic erosion—the classic pharmaceutical life cycle with its precipitous patent cliff is true of the United States but hides the reality of a stronger afterlife in the rest of the world.

3.2.2 Disease

In addition to national market factors, therapeutic market dynamics also play a role in determining likely generic penetration. There are disease states where physicians have little hesitation in switching patients from the brand onto the generic, because the perceived risk of doing so is low and the results of the switch are easy to monitor. A good example would be hypertension. The physician can monitor the patient's blood pressure after the switch and return to

the original brand if unhappy with the performance of the generic. The majority of patients are in no danger if their blood pressure is elevated above its previous level for a week or so. At the other end of the spectrum, a transplant surgeon will be very reluctant to switch a renal patient to a generic. If the generic were not to perform as well as the brand, then the patient might start to reject the transplanted organ and become seriously ill. This has also been the case in the past with epilepsy drugs, where concerns over narrow therapeutic indices and the risk of losing seizure control kept generic penetration rates low. However, when generic competition launched against newer new antiepileptic drugs, such as UCB's Keppra® where the low therapeutic index issues are not so apparent, penetration was still swift and deep, highlighting that even in traditionally "protected" markets, payer pressure will win through.

3.2.3 Size of Brand

All other things being equal, the larger the brand, the more generic companies are likely to enter the market at patent expiry. What is the lower brand sales limit below which no generic is likely to enter the market? As competition heats up in the generic industry, almost any brand is going to attract generic competition. According to analysis presented in Datamonitor's PharmaVitae Explorer, there is virtually no brand sales threshold below which genericization is unlikely to happen; however, there is a definite trend for brands valued at over US$100 million sales to be more severely eroded. In a separate benchmarking study, Datamonitor highlighted that in Germany, after 2 years of generic competition, brands that generated sales of between US$50 and US$100 million per quarter before patent expiry experienced competition from 26 generic manufacturers on average while brands that generated less than US$10 million faced competition from only four generic manufacturers (Datamonitor, "Generic benchmarking: Brand erosion at patent expiry," March 2009, DMHC2496).

3.2.4 Hospital versus Nonhospital Drug Usage

Whether a drug is used in a hospital or retail market can also influence the impact of generic competition, but in two contrasting ways. On the one hand, generic competition can be more intensive for a hospital brand, as the decision makers tend to be hospital pharmacists choosing what to stock rather than individual physicians. Hence, in traditionally brand-loyal markets such as France and Spain, where individual physician preference for brands will limit retail generic erosion, hospital generics can succeed, and indeed this is where many of the first generic players cut teeth. On the flip side, many brands sold into hospitals are already heavily discounted as part of bulk procurement deals, so the price differential between the generic and the brand will often be smaller, creating less of an incentive to use the generic. The net result would

seem to be a slightly higher overall erosion in the hospital space, at least in terms of value.

3.2.5 Active Substance and Other Barriers to Entry

We have already stated that drugs are usually rather easy to manufacture, and that neither manufacturing know-how nor the size of the investment needed to create a copy product is likely to deter a generic competitor. Occasionally, there are exceptions to this rule, with Wyeth's Premarin®, extracted from mare's urine, a classic older example. Fundamentally, such barriers to entry will either come from an ability to source the raw material or to successfully formulate the drug without infringing on patents that remain in place. This latter topic will be discussed later in the book and forms a key tenet of the drug industry's goal of maximizing exclusivity where possible. The branded pharmaceutical industry had hoped that the greater complexity and higher levels of investment necessary to create the generic of a biological would mean fewer generics on the market and thus less sales erosion, and to a certain extent this is true; also, regulatory hurdles are higher for "biogenerics" or "follow-on biologics," and we will look at the special aspects of LCM of biologics later in the book.

One misunderstanding, however, that must be cleared up is the belief that generics companies do not like barrier-to-entry products, and that by raising the barriers to entry companies can deter generic competitors. While this may be true for some mass market generic players, the opposite is actually the case for most of the main generics companies. These companies actively seek out barrier-to-entry products for the very same reasons that brand companies try to raise barriers—to limit the generic competition they will face. For a generics company, being the only generic on the market, or at least one of only two or three players can be the ticket to much higher profits and market share, as price competition will not be as aggressive.

3.3 THE LIFE CYCLE OF A PHARMACEUTICAL BRAND

Bearing in mind all of what we have so far written, let us finish off this chapter by looking at some of the issues we will need to address when designing the lifecycle plan for a specific brand. We will be looking more closely at all of these LCM strategies and all of these questions in detail in subsequent chapters, and we will be offering advice on how to create what we will call an integrated LCM strategy, where the interdependence and timing of lifecycle strategies from cradle to grave will be considered. It goes without saying that each brand will benefit most from a specific portfolio of LCM measures tailored to optimize the life cycle of that particular brand. There is no ideal LCM plan template that can be used blindly for every brand.

Development Phase. Different companies define the border between research and development in different ways, often with a bridging period of "early development" or "translational medicine" linking the two. We will assume that the Development Phase starts at the point at which positive results are obtained in a proof-of-concept (PoC) trial, a small clinical study which has shown that the new molecule is active against a specific molecular target or that it is efficacious in a particular disease state. For molecules that are aimed at targets common to different diseases, the selection of the indication or indications to be included in the PoC trials should already include LCM considerations, although at this stage they should be in the background, and scientific and clinical aspects should determine the population to be studied. Based on the results of the PoC trial, the company will generally decide its lead indication, and considering LCM aspects with new drugs which have the potential to target multiple indications will help ensure that the right decisions are taken regarding indication sequencing, which is one of the most important LCM areas of them all. So what are the questions that we as LCM managers must answer at this early stage of the life cycle? Very importantly, what is the level of resources we are willing to invest in the molecule? Do we want to share the risk—and later the revenue—by taking a development partner? Will we already be investing in follow-on indications and improved formulations during development of the initial indication/formulation, or do we want to manage risk by waiting until we have got a first approval before investing more into the brand, even though this means that the subsequent indications and formulations will not generate revenue until later in the life cycle? Here we need to remember that the first indication to enter development will not necessarily be the first indication to reach market, as different indications demand clinical trials of very different lengths. Our answers to the questions will be influenced by what other drugs we have on the market and in our development pipeline, and we will be looking into that aspect in Part G of this book. Can we identify potential responder and nonresponder patients using biomarkers? Biomarkers may also help us to identify patients that might show side effects. Should we think about parallel development of a companion diagnostic? Would it be best to get to market fast in a limited indication, or invest more time and resources to be able to address a wider patient population right from the start? What clinical trials will be needed to get approval and market access at a premium price? What comparators should we use in our trials? They will have to be drugs that we think our molecule can beat, but they will also have to be drugs that are widely used in our target markets, ideally the gold standard. If we have other advantages, for example regarding convenience, it may be enough to match the safety and efficacy of the gold standard. But this is unlikely to be sufficient if the gold standard is going generic soon after our launch because the price differential will be too

big to be bridged by merely claiming better convenience. And where should we conduct the clinical trials? Probably we will want to select centers in our major target markets, to ensure that awareness of the new brand is high even before launch. Choosing top opinion leaders to run the trials may be attractive, but less so if their centers are overcrowded with other trials which could delay our patient recruitment and thus our launch. It may then be better to look for early adopters who will champion our product as they strive to build their reputations. What clinical end points should we select? They need to be adequate to gain approval, but not so stringent that the probability of success is significantly reduced. What data will be needed to ensure that we get premium pricing? And that reimbursement is granted? And that the drug is listed in formularies? Are we sure that our lead indication will not make it more difficult to get subsequent indications approved, or negatively impact the price for those subsequent indications? One of the additional patient populations we should be considering now are children, as quite apart from incremental sales, there are exclusivity benefits of testing drugs in this often neglected population. Have we looked at the option of seeking an orphan indication, which could also be of advantage if our molecule has a limited patent life as we could obtain orphan drug exclusivity in the main markets? Have we adequately protected the exclusivity of our molecule otherwise? How strong is our primary patent? How broadly have we been able to patent potentially related products from the same drug classes, and especially modifications of our own molecule, to prevent competitors coming to market with me-too products? What is the situation regarding prior art? Do we need additional patents to protect the molecule more strongly, or secondary patents around the formulation, the use, the manufacturing process, and so on? Is our remaining patent life so short that our exclusivity will be dependent on regulatory or marketing exclusivities? If yes, do our indication and formulation strategies, and their sequencing, fully leverage this protection? We certainly do not want to trigger these exclusivities too early if our first indication is small and commercially unattractive and the bigger indications will only follow years later. As the results from our Phase IIb and III clinical trials start to appear, are they what we expected, and do they meet the requirements we set out in advance to enable the project to continue as planned? What is our strategy for publishing the results of the clinical trials, and do these results open any opportunities for additional patents, or point the way to new indications that we did not yet consider? Have we got the dosage and dosage regimen right, and if not, did our clinical design enable us to adapt the trials to adjust for any changes without having to go back and start all over again? How will we position our new brand? What is our pricing and reimbursement strategy? Have we initiated the customer relationship management (CRM) and disease management programs that will ensure maximum uptake of our brand as soon as it is approved?

Introduction Phase. So, we have just passed the first hurdle to success. We have got regulatory approval for the first formulation in the first indication in the first major market. If we have not started to do so already, that event might be enough to persuade us to start investing in follow-on indications and improved formulations, especially if we have got a good price, reimbursement, and formulary listing. If we are in a low-risk organization, if we have very limited resources, or if we are dubious about the chances of success of our brand, we might prefer to wait until the Growth Phase, to see how high sales climb. Only then can we be sure that the brand will generate enough revenue to pay for those additional programs. But the clock is running. How much time will we have to recover our investment in line extensions before the primary patent expires? Were we too cautious, did we wait too long to start those programs? And we may also be kicking ourselves at this point that we were not confident enough to invest earlier in the specific trials that we will need to get approvals in all the major markets. If we are a European or U.S. company, we probably covered both of those continents, but we may have held back with Japan, or China.

Growth Phase. Great! We have got a success on our hands! Sales are now climbing fast. They will be climbing faster, and they will reach a higher peak, if we were brave enough to start some of our LCM projects during the Development Phase. In that case, we will already have a wide geographic spread of sales, we will hopefully have more than one indication approved, and we may already be able to introduce a new, improved formulation which will further differentiate our product from the future competitors which are now being developed. Perhaps we have a new, once-daily form, and the competitors are stuck with twice-daily products. New indications will be most valuable to us when they enable the drug to be prescribed by a different physician specialty, or to a completely different patient population. If a different route of administration was selected for this follow-on indication, or the combination of the drug with a proprietary delivery device was developed, then we could already be building a robust sales base which may not be lost when the basic patent expires. As confidence grows in the use of the drug, it may be dosed higher, and extending the range of available dosage strengths may be a good strategy. On the other hand, if side effects have appeared in some patient groups, it may be advisable to provide a lower dosage strength. Creating a low-dose formulation may also be a good move if we want to create an OTC version of our brand. In indications where multiple drugs are prescribed with a roughly constant dosing ratio, creating fixed-dose combinations may now be an attractive LCM strategy, as it could improve patient convenience and compliance, or even move our product up the treatment hierarchy. At the very least, as we watch the brand franchise grow, consideration should be given to possible follow-up molecules in the same class which are expected to show efficacy and/or safety benefits;

if the benefits are real, and the new molecule different enough from the current one, this strategy could create a new, patented product which will replace the earlier one when its patent expires, while still leveraging the franchise that the company has built within this drug class and physician and patient population. Investigator-initiated trials may be boosting off-label sales in nonapproved indications.

Maturity Phase. Sales may be flattening off now—or at least the growth rate decreasing—as new competitors enter the market. But the far bigger risk to the continuing growth of many brands is likely to be the approaching expiry of the primary patent. As mentioned earlier, many brands never even experience a Maturity Phase, and the patent expiry hits them while sales are still growing strongly. Too often, the few years—or even the few months—before patent expiry is the time that some companies first start to think about late-stage lifecycle management (LLCM), and how they can maintain brand exclusivity for longer or retain more market share after exclusivity is lost. Very often, this is too late to put these ideas into practice before patent expiry. Some drugs may be able to rescue at least part of their sales from the impending plunge by moving to non-prescription, OTC status. It is now that brand companies, sometimes in desperation, start implementing last-minute strategies to try to delay generic entry to the market for as long as possible. The European Sector Inquiry called these strategies the "toolbox" that branded companies use shortly before exclusivity is lost in an attempt to save their doomed brand franchise. We will be looking at all of these strategies later—including raising purity and bioequivalence standards, submitting citizen petitions and white papers, trying to cut deals with the generic companies, authorized generics, spurious litigation, and much more. The purpose of the branded drug company is usually not to win against the generic threat, as this is in most cases not a realistic option, but to lose later and preferably against less generic competitors! Just before patent expiry, brand sales may be at their highest ever and profits almost certainly are, as marketing support will have largely been withdrawn in favor of newer brands in the product portfolio. For a brand selling for US$2 billion per year, with a margin of as much as 75% at this late stage, it is a simple calculation to see that every additional day of exclusivity is worth more than US$4 million profit!

Decline Phase. Despite all of our efforts, the bad thing has finally happened. Exclusivity has been lost, and generics are flooding the market. In most cases, there is little point cutting the brand price to try to chase the generics down into the basement, as the generic companies have leaner structures and lower profit margins, and can always go still lower. We will probably maintain the premium price of our brand and concentrate our efforts on the laggards. Sales may hold up rather well in countries with less sophisticated ways of forcing generic substitution, and especially in

self-pay markets. Companies that are good at LCM and have thought far enough ahead may have secondary patent-protected new formulations on the market which offer enough real benefit over generics of the old formulation to get a significant share of prescriptions of the drug. But the hurdle for doing this is already high, and it is getting higher, and generic companies are becoming very efficient at designing around formulation patents. In those cases (the majority) where most of our brand sales are lost to generics after primary patent expiry, the brand will now just be managed for profit. Marketing support will be cut right back (the laggards will continue to use the brand anyway), the number of product variants will be pared to reduce manufacturing costs, and manufacturing may be moved to a low-cost country or contracted out to a third party (perhaps even to one of the generic competitors). Another possible strategy—the exact opposite of allowing a third party to manufacture the brand—is for the brand company to manufacture product for one or more of the generic companies, a so-called licensed generic. Some local LCM (e.g., new formulations) may persist in large, self-pay markets, where development costs and local regulatory hurdles are low, but generally central R&D support of the brand will be cut almost to zero. Finally, as time progresses, the brand sales drop to a level where the bother of keeping it on the market is bigger than the profits. The brand may now be withdrawn from the market, or sold or licensed to a smaller company which can make a living by selling minor brands.

In following a typical brand through its life cycle in this way, we have divided up LCM measures according to lifecycle phase. But it is evident that many of the individual measures can be applied at different stages in the life cycle. For example, a new indication may be developed concurrently with the first indication, or it may be developed during the Introduction or Growth Phases to boost sales in the middle of the life cycle, or it may be developed in the Maturity Phase when, in association with a new route of administration or some form of drug delivery device, it may be able to retain more market share from generics once the primary patent expires.

Another way of classifying LCM measures would be to look at what goals they are intended to achieve in the life cycle. Related to brand sales, there are seven possibilities:

1. Faster market introduction
2. Steeper growth curve
3. Shorter time to peak sales
4. Higher peak sales
5. Longer exclusivity
6. Slower sales decline after exclusivity loss
7. Higher brand market share after loss of exclusivity.

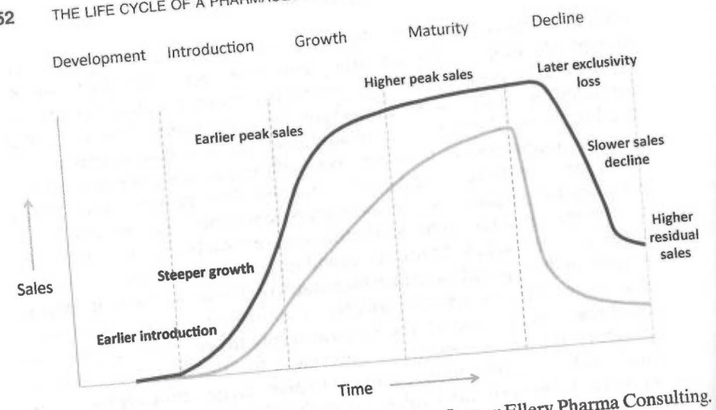

FIGURE 3.2. Effects of LCM on the lifecycle curve. *Source*: Ellery Pharma Consulting.

Expansive	Defensive	Preparative
Maximize the product's value *throughout its lifecycle*	Maximize the product's value *at peak or patent expiry*	*Prepare for new portfolio entrants and maintain market share*
Entering a new market • Gain market share • Increase sales **Approval for subindication** • Increase market share • Increase sales **New formulation/combination** • Increase market share • Grow market • Increase sales	**Second or later to market for a subindication** • Maintain market share • Increase share versus other competitors **Equivalent formulation to a competitor** • Maintain market share • Increase share versus other competitors **New formulation/combination** • Switch existing patients to new formulation to maintain share after generics entry **New data** • Maintain share of voice • Maintain market share	**New data** • Maintain share of voice **Pricing change** • Maintain market share in anticipation of new launch/ generic entry

FIGURE 3.3. LCM tactic goals—expansive, defensive, and preparative. *Source*: Datamonitor.

Figure 3.2 shows these different purposes of LCM. It is important to note that Figure 3.2 only considers sales and not profit.

Again, a specific LCM measure could serve several of these different needs. For example, a sophisticated new formulation may get a higher price and this may lead to higher peak sales, and if securely patented, it may lead to a slower sales decline and a higher market share after patent expiry.

Yet another way of classifying LCM strategies is that used by Datamonitor, as shown in Figure 3.3. Datamonitor divides LCM strategies according to

whether they are "expansive," "defensive," or "preparative," reflecting the primary goals of the tactic or strategy in question.

For this book, we have decided to categorize LCM measures according to the functional department in the company that is likely to have the lead responsibility for a particular measure. This has the advantage in a long book of this kind that it enables functional specialists to concentrate on "their" chapters, while at the same time seeing how their efforts can contribute to the overall LCM program for a brand.

It is important to understand that this structure of the book is not intended to support the view that LCM is a decentralized process that should take place within the individual functions. Nothing could be further from the truth! An effective LCM program requires the highly cross-functional collaboration of a whole range of functional experts, as we shall see later when we discuss organizational aspects of LCM.

We will be looking at a whole range of potential LCM measures in the following chapters. This will include

- Legal/regulatory measures:
  - Patents
  - Regulatory exclusivities
  - Litigation and settlements
- Developmental measures:
  - Indication expansion and sequencing
  - Dosage strengths and regimens
  - Reformulation and combinations
  - Delivery devices
  - New route of administration
  - Biomarkers/diagnostics
  - Raising technical hurdles for generics
  - White papers and citizen petitions
  - Next-generation products
- Commercial measures:
  - Geographical expansion and optimization
  - OTC switching
  - Brand loyalty and service programs
  - Strategic pricing
  - Generic strategies (in-house, licensed, or authorized)
  - Divestiture/product withdrawal

But before we start looking at all of these measures individually, it is essential that the reader fully understands four important environmental factors that

strongly influence LCM efforts, particularly in the largest pharmaceutical markets, the United States and the European Union. The next four chapters will focus on these factors, which are:

1. The Generic Approval Process (Chapter 4)
2. Hatch–Waxman Legislation and Its Effects on LCM (Chapter 5)
3. U.S. Health-Care Reform 2010 (Chapter 6)
4. European Sector Inquiry (Chapter 7)

PART B

LIFECYCLE MANAGEMENT REGULATORY AND LEGAL ENVIRONMENT