

Challenges Facing the Branded Drug Industry

In 2004, Capgemini conducted an industry-wide survey on pharmaceutical lifecycle management (LCM) (“Increasing the lifetime value of pharmaceutical products,” Capgemini Vision & Reality Research, 2004). They held a series of interviews with pharmaceutical industry executives, asking them how important LCM had been for their business in the past 5 years and how they expected its importance to change during the coming 5 years. As can be seen in Figure 1.1, these executives felt that LCM had been important, but 90% predicted that its importance would grow during the 5 years following the publication of the report (2006–2010), with 60% expecting it to become much more important.

Today, just after the time horizon of this prediction, we can look back and state that it has proven to be very accurate, with more and more attention paid to LCM in company statements, conferences, and industry reports.

Why did these executives expect LCM to gain in importance, and why has their prediction proven to be correct?

To set the scene for any discussion of LCM of pharmaceuticals, it is essential that one fully understands the challenges facing the branded drug industry. On the one hand, many of these factors are drivers of the increased interest in LCM; on the other hand, some of the factors actively discourage LCM and put into question the sustainability of certain LCM strategies that were successful in the past.

As we see it, the main challenges are the following:

- Depleted new molecular entity (NME) pipelines/lower R&D efficiency
- Higher development costs
- Safety concerns
- Tougher environment for pricing, reimbursement, and listing

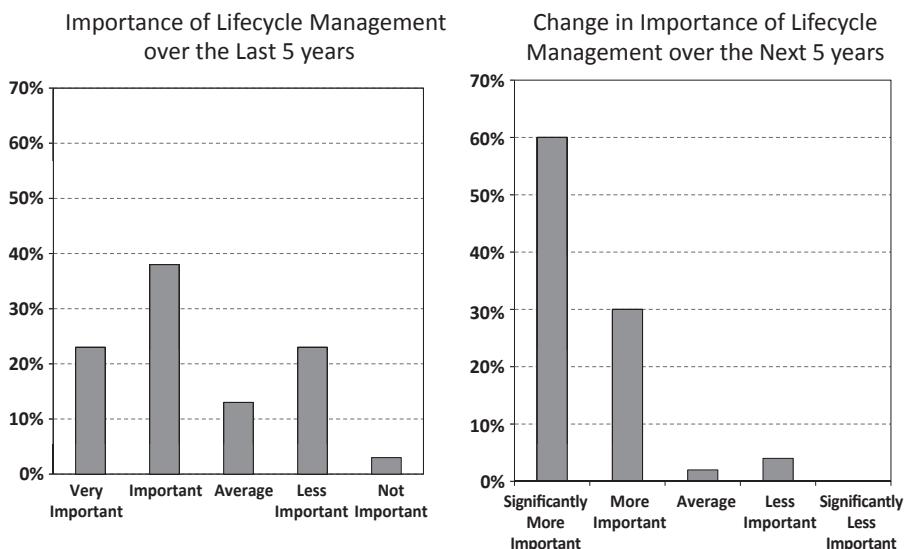


FIGURE 1.1. Increasing importance of lifecycle management. *Source:* Capgemini 2004 Vision & Reality Research, 60 Responses.

- Increased competition
- Earlier genericization
- Faster sales erosion following patent expiry
- Poor image of branded drug industry
- Diversification

1.1 DEPLETED NME PIPELINES/LOWER R&D EFFICIENCY

Since the mid-1990s, the number of NMEs approved by the Food and Drug Administration (FDA) and other health authorities has been declining, as shown in Figures 1.2 and 1.3. In the period from 2006 to 2010, the FDA approved half as many NMEs as in the period 1996–2010.

There is also mounting concern that many of the NMEs that do reach market are not adding significantly to the value of what is already there. In other words, the lack of innovation is not only quantitative in terms of the number of approvals and launches, but also qualitative in terms of the level of innovation as it translates into value for the patient.

A good example of this can be found in the treatment of hypertension. There are two levels at which we can consider “me-too-ism”: first, at the level of the drug class, and second, at the level of the disease. Until recently, there were five classes of safe and effective antihypertensives on the U.S. and

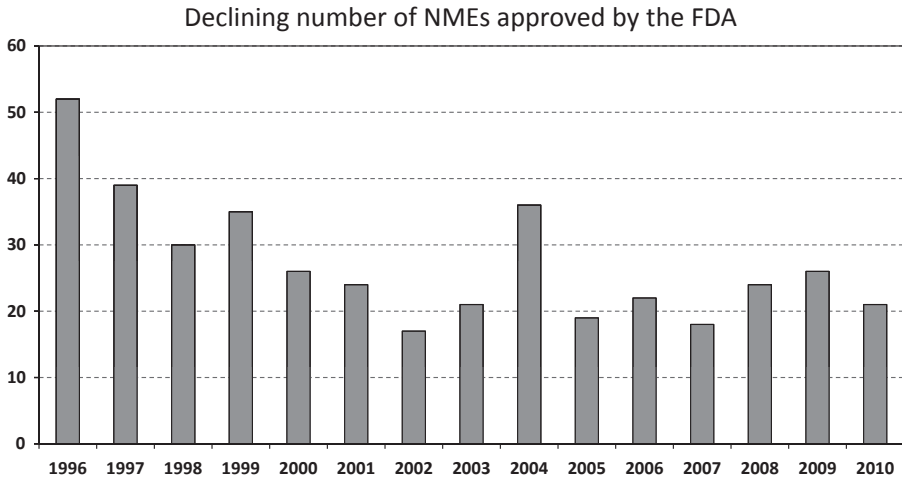


FIGURE 1.2. Reducing R&D productivity—Approvals. *Source:* www.fda.gov.

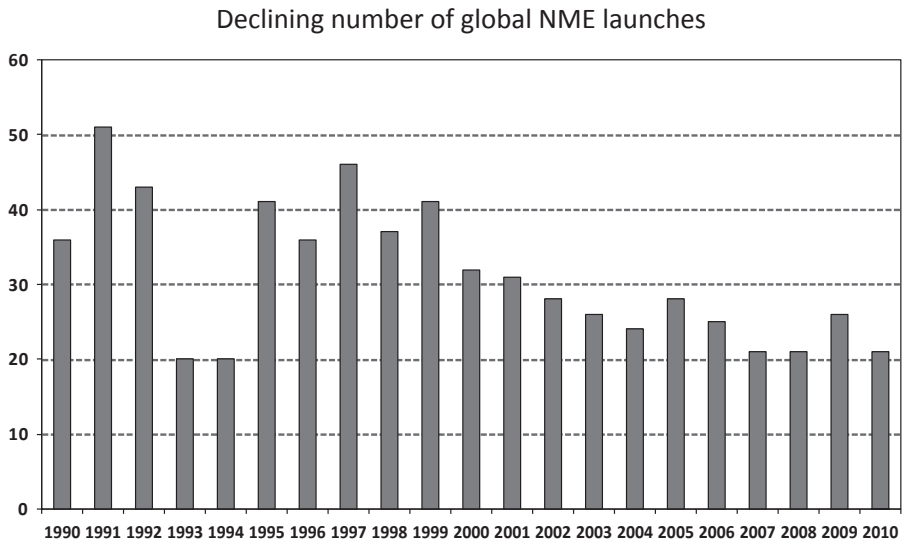


FIGURE 1.3. Reducing R&D productivity—Launches. *Sources:* www.fda.gov & www.pharmatimes.com.

European markets: the beta blockers, ACE-inhibitors, angiotensin receptor blockers (ARBs), Ca-antagonists, and diuretics. Well over a dozen different beta-blockers are available, over a dozen diuretics, and a good half-dozen each of ACE-inhibitors, Ca-antagonists, and ARBs. Some duplication in each class is acceptable from the medical perspective, as different patient groups may

respond differently even if there are only tiny variations in the molecular structure of the drugs, but this high level of duplication was not driven by patient need, but by the commercial reality that large companies with a stake in cardiovascular medicine wanted to have their own patented drug in this highly profitable indication. Big Pharma will explain the duplication somewhat differently, particularly emphasizing two aspects which do also indeed play a role:

- Medical breakthroughs are rarer than incremental improvements of existing drugs. The later beta-blockers, for example, are in some cases safer and/or more efficacious than the earlier ones.
- More drugs of the same class on the market mean more competition and therefore lower prices. (This argument does, of course, lose some credibility when a company fights to preserve exclusivity on its brand even after other representatives of the same drug class have already gone generic.)

This, then, is duplication at the drug-class level. Duplication at the disease level is also well illustrated by referring to the hypertension arena. Although all five of the drug classes mentioned above are now available as cheap generics, the first representative of a new class of drug, the renin inhibitors, has already entered the market, and others are bound to follow. In reality, of course, the blood pressure of the vast majority of patients with hypertension can be effectively brought under control using the existing, genericized drugs, either singly or in combination. Companies have continued to invest in hypertension not because it is an unmet need, but because it is a big market, and it is easy to test the drugs. The real solution to the hypertension epidemic does not, of course, lie with better drugs. Stopping smoking, more exercise and less calories and alcohol, better monitoring of the population to ensure that hypertensive patients are identified, and identified early, more aggressive therapy by physicians using existing drugs, and better compliance by patients are vastly more important factors than new drug classes. Clearly, patient needs would be far better served by investing in these aspects rather than by developing me-too NMEs or new drug classes which are barely distinguishable in their clinical effects from the ones already on the market.

Analyzing all of the reasons for the lack of true innovation in drug research would go beyond the scope of this book. Many theories have been advanced, and the truth is likely to lie in a combination of different factors. Here are some of the leading contenders:

- *No More Low-Hanging Fruit:* As already mentioned, there are already safe and effective therapies available for most “easy” diseases, hypertension being a prime example. The diseases which still have a high degree of unmet need, for example, cancer, mental disease, and degenerative diseases of old age, have complex etiologies and are more difficult to treat. One CEO put it like this: “Most of the easy wins have already been

made. . . . Now we are into more indirect ways of treating diseases: stopping tumours from growing by preventing their ability to get blood supply. These are much more complicated. This is not to belittle the advances so far, but things are getting difficult” (Lars Rebien Sorenson, CEO of Novo Nordisk, *BusinessWorld*, 2004). Pipeline attrition is of growing concern at both ends of the development process. Early on, better validation of molecular targets for their relevance in man is required to prevent the high rates of efficacy and safety failures. And where projects do fail, the problems must be recognized earlier in the development process. Phase III attrition, and thus the loss of drugs or indication extensions after most of the huge development costs have already been incurred, represents a massive opportunity cost that the branded drug industry can scarcely afford. In 2010—just in cancer—Big Pharma experienced 10 Phase III failures (Pfizer: Sutent® and figitumumab, AstraZeneca: cediranib and zibotentan, Amgen: Vectibix®, Novartis: Zometa® and ASA404, Lilly: Alimta® and tasisulam, Roche: Avastin®).

- *Low Innovation in Big Organizations:* The huge research departments of Big Pharma may not be the ideal breeding ground for innovation, which is more likely to take place in smaller, less structured, and more autonomous groups. This is frequently advanced as an explanation as to why small biotech companies appear to have a better innovation record than the larger companies, and why many Big Pharma companies are closing more and more biotech deals while cutting back on their internal R&D resources. Pfizer, GlaxoSmithKline (GSK), and Novartis are three of many examples of companies that made massive cuts in 2010 and 2011. For years, companies have sought a solution by pursuing megamergers and frequently spoke of “critical mass” in R&D. The trend is now in the opposite direction, with companies breaking their R&D forces into smaller, more autonomous groups, outsourcing and relying increasingly on biotech for innovation. One example of the failure of megamergers to provide the necessary impulse is evident at GSK. The two premerger companies Glaxo Wellcome and Smith Kline Beecham together received 26 NME approvals in the United States in the 6 years prior to their year 2000 merger; in the 6 years following, the merged company, GSK, only managed 15 NME approvals. Another aspect of this problem may relate to executive compensation. In a press release in March 2011, Hay Group consultants stated that biotech and biopharma are innovators not only in the technology and products coming out of their labs, but also in how they measure and reward their executives. Senior executives in Big Pharma are incentivized for the most part to achieve short-term financial results, and this would seem to be inappropriate in an industry with extremely long, multiyear product development cycles.
- *Delayed Peak Sales:* The achievement of peak sales of new introductions is frequently delayed by restrictions of their use to small, high unmet need patient subpopulations until a comprehensive safety database has

been accumulated to allow use in broader patient populations. Together with downward pressure on prices, this leads to less funds being available to pump back into R&D.

Whatever the exact contributory effect of these different causes, it is an undisputed fact that less new NMEs are making it to market, and this inevitably means that companies are forced to attempt to squeeze more value out of their existing marketed brand assets.

As we finalize this book, there are early signs that things might be improving. At a Reuters Health Summit in New York in May 2011, the Head of FDA's drugs center, Janet Woodcock, stated that as the FDA had already approved 12 new drugs to date in 2011, she expected last year's total of 21 to be surpassed. She felt this was due to more successful products coming from advancements in science and research investments made a decade or more ago, but added that although she thought that the nadir had been reached, recovery would be gradual. Indeed, by early December, the FDA had approved 30 NMEs, the highest number since 2004. We shall have to wait to see whether this is the start of a new positive trend or the kind of one-off blip that 2004 turned out to be.

1.2 HIGHER DEVELOPMENT COSTS

Although the profit margins of branded drug companies are under increasing pressure, it is important to realize that the reduced number of NMEs reaching market cannot in any way be blamed upon a reduction in R&D budgets, at least up until very recently. Indeed, as can be seen in Figure 1.4, R&D budgets increased steadily during the past quarter century. A simple calculation from Figure 1.4 shows that it cost about US\$350 million to put one NME onto the market in 1990, with this figure climbing to US\$2.5 billion per NME in 2007. In other words, the efficiency of R&D has dramatically reduced in the last 20 years.

So what are the true costs of developing an NME? Many people were skeptical when, in 2004, the Tufts Center for the Study of Drug Development estimated the costs of bringing a new NME to market as US\$800 million (PhRMA, Tufts CSDD Analysis, 2005). This figure included the costs for all of the developmental drugs that did not make it to market, and the direct costs of development were more likely to have been around half of this figure, or US\$400 million. And then in 2006, Tufts announced that it had developed the first comprehensive estimate of the average cost of developing a new biotechnology product, and pegged it at US\$1.2 billion (PhRMA, Tufts CSDD Analysis, 2006). About half of this sum was needed in preclinical development, the other half for clinical trials. Again, one can discuss whether these are the correct figures. What one cannot dispute is that the costs of development are very high, and still climbing.

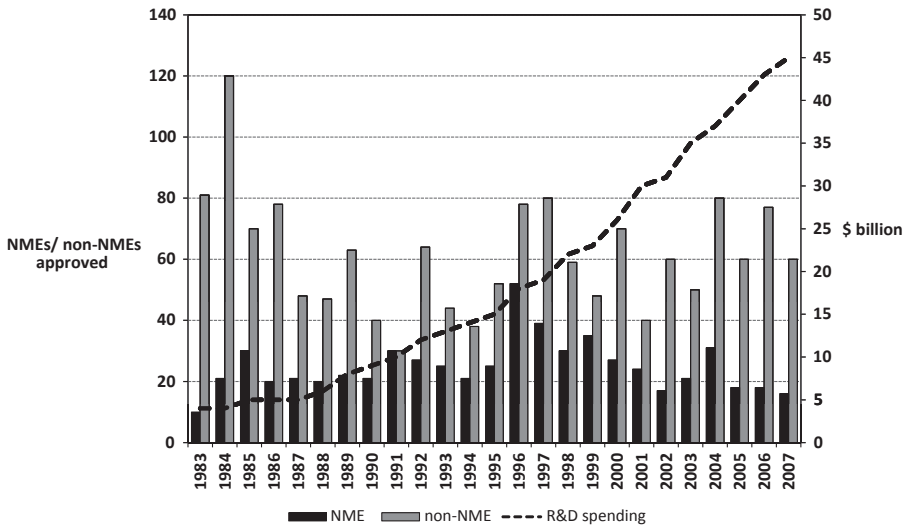


FIGURE 1.4. Increasing R&D spending is not reflective of the number of new NMEs.
Source: FDA.

Obviously it costs less, and usually a lot less, to develop a line or indication extension of an already marketed NME as part of an LCM strategy. Even in the case of a completely new indication, much of the preclinical work performed for the initial approval can be reused for the new regulatory submission. Added to this, attrition is lower as the molecule is better understood, and there are less likely to be surprises regarding its safety and efficacy. Moreover, the commercial risks following approval are also more manageable because the drug has already been on the market, and its acceptance by health authorities, payers, physicians, and patients is well understood.

1.3 SAFETY CONCERNS

Regulatory requirements for NMEs have increased dramatically in recent years. This means higher development costs per NME and thus, inevitably, less projects and less NMEs. Some of this trend is driven by more stringent health authority demands regarding efficacy and quality, but the overwhelming majority of the increased per-project investment is caused by an increase in safety requirements.

Because of a series of high-profile product withdrawals resulting from safety problems that were not observed or not taken seriously enough during development (e.g., Bextra®, Lipobay®, Vioxx®, and Zelnorm®), more NMEs are being lost in preclinical development as a result of weak or ambiguous safety signals which in the past would not have caused a project to be discontinued.

But late-stage attrition in Phase III trials is increasing as companies sometimes do not realize—or do not want to accept—that their NME will not make it to market. This is an inevitable consequence of depleted pipelines, as there are likely to be less short-term alternatives to the projects in Phase III and therefore tremendous financial pressure to make the few available options a success. Once a drug has reached Phase III, most of the development costs have already been incurred or committed, so such late-stage failures are much more damaging than failures early in the project because of the high sunk costs and the opportunity costs of not having been able to invest in alternative profit-generating activities that might have been successful. The rejection of a regulatory dossier is, of course, even more damaging as by that time, significant funds will probably already have been invested in manufacturing capacity and premarketing activities.

Let us look at just one example of how this increased focus on safety can hit a company. The company was Novartis, and the year was 2007. In February, Novartis received the first blow—an approvable letter from the FDA for its DPP-4 inhibitor, Galvus®, where the company had hoped for a straight approval. FDA was concerned about skin lesions seen in monkeys, and also wanted to see additional data regarding use of the drug in Type 2 diabetes patients with severe renal problems. Analysts assumed that the failure to get an approval letter would delay the market entry of Galvus by at least a year, and that this would allow Merck's DPP-4 inhibitor Januvia® to build a dominant market leadership position, but by the end of the year, things looked even worse for Galvus, and Novartis was admitting that the drug might never reach the U.S. market. That prophecy turned out to be correct, although the drug did get approval in Europe and many other countries and generated sales of close to US\$400 million in 2010, more than doubling the previous year's result. The second blow in 2007 came in March, when the FDA requested that Novartis withdraw from the U.S. market its irritable bowel drug, Zelnorm, after analysis of clinical trial data had revealed a higher incidence of cardiovascular side effects in patients receiving Zelnorm than in patients receiving placebo. Still Novartis's miserable year was not finished, and in September, the company received a nonapprovable letter from FDA for its COX-2 inhibitor, Prexige®. Again the issue was safety, with the FDA concerned about the death of two patients in Australia suffering from liver disease, and in any case sensitized to the whole COX-2 inhibitor drug class following the withdrawal of Vioxx. All three of these 2007 decisions to withdraw or not to approve Novartis drugs were based on safety data which were far from black and white. Although these things are hard to prove in retrospect, a few years earlier—prior to the withdrawal of Vioxx—it is very likely that these data would not have been interpreted as strictly, and that all three drugs might well now be on the U.S. market. Moreover, during the same period, three other Novartis products were also labeled with black-box warnings (Elidel®, Myfortic®, and Tasigna®). The negative decisions by the FDA must have cost Novartis many billions of U.S. dollars in cumulative sales, and the value of Novartis shares dropped by 18% in 2007.

More recent examples of the increasing focus on safety issues can also be cited. The sales of GSK's Avandia® in Europe were suspended in 2011, and its use in the United States restricted to Type 2 diabetes patients who have both failed on every other diabetes medicine and have been made aware of the drug's substantial risks to the heart, which include stroke and heart attacks. Avandia's main class rival, Takeda/Lilly's Actos®, did not escape the crackdown on safety either, with concerns over a potential higher incidence of bladder cancer leading to withdrawals in Germany and France, and an eventual strong warning across the rest of Europe. And it was not only the older drugs that felt the impact of caution on safety of antidiabetic agents. In June 2011, an FDA advisory committee voted against AstraZeneca/BMS (Bristol-Myers Squibb)'s first-in-class SGLT2 inhibitor dapagliflozin on the evidence of potential increased cancer risks with the new agent.

Indeed, older, established brands are frequently perceived as safer than newer drugs, although this judgment should in reality be considered suspect and frequently does not stand up to close scrutiny. After all, the older drugs were not subjected to the same level of safety testing during development as is today the case. It is indeed interesting to speculate whether companies today would have persisted with the development of such therapeutic mainstays as penicillin and aspirin. Penicillin is associated with a 5% rate of hypersensitivity reactions and a 1% likelihood of anaphylaxis, and aspirin can cause gastric bleeding and intracranial hemorrhage. Recently, a meta-analysis was performed of 31 clinical trials involving more than 116,000 people taking either naproxen, ibuprofen, diclofenac, Pfizer's Celebrex®, Merck's Arcoxia® or Vioxx, Novartis's Prexige, or a placebo. All of the drugs were associated with a higher risk of stroke, heart attack, or cardiovascular death. While Vioxx showed the highest risk of heart attack (2.12 times compared with placebo), it was Arcoxia (4.07) and diclofenac (3.98) that posed the highest risk of cardiovascular death (Trelle, S., Reichenbach, S., Wandel, S., et al. 2011. "Cardiovascular safety of non-steroidal anti-inflammatory drugs: Network meta-analysis." *BMJ*). While Vioxx was withdrawn from the U.S. market in 2004 and Arcoxia received a nonapprovable letter from the FDA in 2007, diclofenac remains on the market after over 30 years as one of the most successful drugs in history, with the original brand, Novartis's Voltaren®, topping US\$700 million in annual prescription sales in 2010.

Health authorities have been heavily criticized for allowing "dangerous" drugs to reach market in recent years, and there can be little doubt that they see less potential for criticism if they allow older drugs to continue to be sold than if they allow new ones with potentially serious side effects to reach the market. Thomas Paine explained the phenomenon rather elegantly in his 1776 book, *Common Sense*, when he stated that "A long habit of not thinking a thing wrong gives it a superficial appearance of being right. Time makes more converts than reason."

But companies must still be cautious of what they claim for their older drugs; Pfizer was warned by the FDA in June 2010 for failing to promptly

report serious and unexpected potential side effects from several of its marketed drugs. In a letter to Pfizer CEO Jeffrey Kindler, the FDA cited a series of examples involving some of the company's top brands, including Viagra®, Lipitor®, and Lyrica®. According to the FDA letter, the delays in reporting side effects stretched back to 2004 and had increased in recent years. The letter stated that "FDA expects drug manufacturers to establish and implement reasonable mechanisms to assure that all serious and unexpected experiences are promptly recorded and investigated."

1.4 TOUGHER ENVIRONMENT FOR PRICING, REIMBURSEMENT, AND LISTING

Once upon a time, a company only had to prove that its new drug was safe and efficacious, and premium pricing and reimbursement were more or less guaranteed. Of course, it was usually preferable to be the first representative of a new class, but me-too molecules did just fine as well. Almost any slight advantage over the existing therapies, however tentative, was honored with a good price, wide reimbursement, and formulary listing. Decision making regarding which drug to use in a particular case was decentralized, with the physician acting as the sole key decision maker, and companies strove to influence the decision to prescribe their drug with expensive marketing campaigns, huge sales forces, and—until they were banned in most developed markets—all manner of incentives for physicians to prescribe one particular drug rather than its competitors. Pharmacies were compelled to fill the prescription as written, even if a generic was available, and in any case, pharmacy profit margins were likely to be higher on the original brands.

The world is changing fast in the developed markets. A few extracts from the IMS Institute for Healthcare Informatics report regarding drug usage in the United States during 2010 can serve to underline this new situation:

- Spending on prescription medicines increased by the historically low figure of 2.3% in 2010 compared to 5.1% the year before.
- The total volume of medicines consumed in oral or nasal form increased 0.5% in 2010, representing a decline of 0.3% on a per capita basis due to lower or declining demand in nearly every major therapy area.
- The number of visits to doctor offices was down 4.2% in 2010. The number of patients starting new treatments for chronic conditions declined by 3.4 million.
- The average cost of oral medicines declined 0.1%.
- Of the 4 billion prescriptions filled through retail channels, chain drug-stores were increasingly chosen by patients, reflecting both the convenience of these pharmacies and the availability of discounted generics.

- Average spending per new branded product (<2 years on the market) was US\$62 million in 2010, down from US\$114 million in 2006, reflecting a shift in the mix of new products toward orphan drugs and medicines with the same mechanism of action as existing treatments.
- Spending on brands declined 0.7%, while spending on branded and unbranded generics rose 4.5% and 21.7%, respectively. Generics accounted for 78% of all retail prescriptions dispensed.
- On average, more than 80% of a brand's prescription volume were replaced by generics within 6 months of patent loss.

OECD Health Data for 2010 shows that the problems are not limited to the U.S. market. Here are some extracts from their reports:

- Health-care costs are increasing everywhere and will continue to rise. The overall trend is that the growth in health-care costs is exceeding economic growth and necessitates health-care reform.
- In every OECD country except Mexico and the United States, the bulk of health care expenditures come from public funding. A trend of convergence is occurring, with some countries decreasing their public spending while others are increasing theirs.
- Pharmaceutical costs make up the bulk of health expenditures on medical goods in OECD countries, at an average of about 20%, the number ranging from 11% to 38%. In 2007, pharmaceutical spending amounted to 15% of the total health-care expenditure across OECD countries, and the average per capita expense had risen by almost 50% over the preceding 10 years.

So although drug prices are only responsible for a relatively small proportion of total health-care costs, this proportion is growing, and this is one factor which makes drug prices and usage a major target all over the world in government attempts to reduce the spiraling costs of health care. At least part of this overemphasis on drug prices and usage is fueled by the current unpopularity of and lack of trust in the drug industry, and we will discuss this important issue later.

It used to be the case that a company only had to prove safety, efficacy, and quality to obtain approval for and market a new drug. Now it is no longer enough to prove that a drug is safe and effective to be sure of regulatory approval and commercial success. Today, that drug will only gain premium pricing, reimbursement, and listing if a comprehensive battery of health economics studies has been included in the development program. Over and above mere "efficacy," these studies must be capable of proving the effectiveness and cost-effectiveness of the new drug in the real world. Even then, there are no guarantees that the drug will actually be used, as it will only be purchased if there are not more urgent calls on the health-care budget.

Health economics studies are essential for getting pricing and reimbursement

Regulatory	Pricing and reimbursement	Purchase
<ul style="list-style-type: none">• Safety• Efficacy• Quality	<ul style="list-style-type: none">• Effectiveness in the real world• Cost-effectiveness (value for money)	<ul style="list-style-type: none">• Budget impact

FIGURE 1.5. Importance of health economic studies. *Source:* Ellery Pharma Consulting.

Figure 1.5 summarizes the different levels of studies that are required before a new drug will actually get used.

As mentioned in the OECD extract cited earlier, currently in the United States, there are no government price controls over private sector purchases. However, federal law does require pharmaceutical manufacturers to pay rebates on certain drugs to be eligible for reimbursement under several state and federal health-care programs.

While the United States relies mainly on competition to keep downward pressure on the price of drugs, all other major OECD countries practice price control in one form or another. The mechanisms employed vary considerably between countries, but the aim is always to achieve a reduction of drug budgets. It goes beyond the scope of this book to conduct a comprehensive global analysis of drug pricing and reimbursement, but we will spend some time looking at this important area as the measures can also impact LCM strategies like new formulations and fixed-dose combinations. Depending upon the market, the methods used include company profit control, price cuts and price freezes, reference pricing, prescription restrictions, physician budgets, patient co-pays, or self-pays, health economics analyses, parallel trade, tendering, generic substitution, and over-the-counter (OTC) switching. Price controls can be applied at the manufacturing or at the retailing level.

The most direct control is to set a fixed sales price and not allow sales at any other price. In other cases, governments will set very low reimbursement prices so that the patient has to pay the excess to the real price; this encourages the patient to look for a cheaper alternative, and this would be a generic if one is available. Some governments, including Japan and Canada, regularly reduce the reimbursement prices of marketed drugs.

Reference pricing is the preferred method for keeping prices down in some countries, where the government sets the level of reimbursement based on that in another country or basket of countries. Or the government may set reimbursement at the level of the average or lowest price of other drugs in the same therapeutic class. This last practice has been strongly criticized by

the branded drug industry because it undervalues the properties of new market entries in existing classes, although these in some cases have efficacy or safety advantages, or may be more suitable than existing brands for treating certain patient subgroups. This form of reference pricing often penalizes new formulations, setting their prices at the same level as the generic of the original formulation.

Another method used to restrict usage of expensive new drugs is to limit the quantity that can be sold. Alternatively, a higher price may be allowed if low volumes are sold, but the price is cut if the sales volume rises above a predetermined level.

Actually limiting the amount of profit that a company is allowed to make on a product is an effective indirect way of controlling price and volume. This is practiced, for example, in the United Kingdom.

These measures all affect pricing and reimbursement. But as stated earlier, getting a price and reimbursement is not the last problem that a drug must overcome to be commercially successful.

The next hurdle is actually getting onto the formulary, that is the list of drugs that the government, hospital, or insurer is willing to purchase and/or reimburse. A drug which is not included in the formulary will not get prescribed or dispensed unless an exception is granted, and this is hard to achieve. Even in situations where drugs not included in the formulary can be legally prescribed, the fact that they are not reimbursed will severely limit usage.

NMEs and LCM measures such as new indications and new formulations will be subjected to exactly the same kind of cost containment pressure at the price, reimbursement, and listing levels. Getting significant usage of line extensions at a premium price over the original product is becoming increasingly difficult, and in many cases, health economics studies are likely to be required which are so expensive, and so uncertain in their outcome, that the line extension does not offer an attractive commercial opportunity. However, line extensions can benefit to some extent from the experience already gained with the molecule on the market. The concerns of payers will be known and understood, and in some cases, arguments may already have been found or data already generated to address these concerns. In addition, if positioned and designed correctly, as we will see in later chapters, such line extensions can improve the value proposition and thus the formulary status of a whole franchise. The risk of failing to get a return on investment in developing a line extension may thus still be less than for an NME.

Pricing and reimbursement pressure is not going to go away. Indeed, it shows every sign of increasing in every developed market. Let us look at Europe first. Even as we finalize this book, it is uncertain whether the main European currency, the Euro, will survive, or whether countries with weaker economies such as Greece will have to revert to their old currencies, with enormous financial implications of doing so. The problems started in Greece, Ireland, and Portugal but have now spread to Italy and Spain, with the rating agencies even casting a critical eye on the situation in France and Germany.

It is indeed staggering to look at the levels of debt that most western countries have accumulated. Within the Eurozone, Spain, France, and Italy each have total debts (government, nonfinancial business, household, and financial institutions) of between 300% and 400% of GDP. This compares with figures of 400% for the United Kingdom (which is not in the Eurozone, having retained the pound sterling as currency), 300% for the United States, and nearly 500% for Japan. The healthiest European Union (EU) economy is Germany, but even here debt is at the same level as in the United States. The ratings agencies Standard and Poor's and Fitch have responded by downgrading or placing on credit watch all of the Eurozone economies. Eurozone economies which have already lost the top AAA Standard and Poor's rating include Belgium, Greece, Ireland, Italy, Portugal, and Spain, while it is worth remembering that both Japan and the United States are also not rated AAA.

Moreover, Japan, the second biggest drug market in the world behind the United States, is currently coping with the aftermath of the catastrophic March 2011 earthquake and the ensuing nuclear plant problems in Fukushima, and facing rebuilding costs estimated to be in excess of US\$300 billion.

As we write, it is not clear how these various crises will play out, but—looked at from the narrow perspective of our book—they are bound to both increase price pressure on pharmaceuticals as countries all over the world fight to contain public spending and increase the pressure on funding in new product development. This latter factor will particularly impact biotech and other R&D-focused organizations as previous sources of funding become more difficult to find.

1.5 INCREASED COMPETITION

It is helpful to consider competition at three different levels:

Molecule. The company must compete with other companies offering the same molecule once the patent has expired, been invalidated, or been infringed “at risk” by a generic company. This form of competition has grown much stronger in recent years and will continue to do so, as we shall see in later sections of our book.

Drug Class. The company must compete with other companies offering different molecules in the same drug class. The dearth of innovative new classes of drug has driven ever more companies to develop “me-too” drugs, in other words, drugs that are in the same class but are claimed to offer some advantage regarding efficacy, safety, or convenience. This is not a new phenomenon, as the period of time that the first drug of a new class will have the market to itself before the next entry in the same class arrives has been growing shorter for decades; this trend is shown in Figure 1.6.

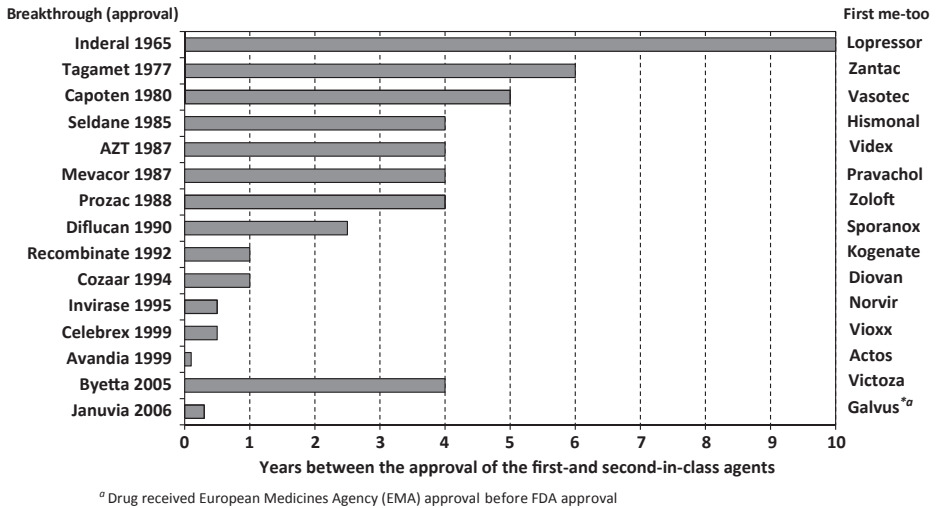


FIGURE 1.6. Delays getting shorter to second-in-class entries. *Source:* Adapted from Wilkerson Group, 2000.

Disease. The company must compete with other companies offering solutions for the disease which lie outside of the drug class. This can be a very broad competitive arena and can be divided into two sublevels:

- Competition with other prescription drug classes
- Competition with therapies other than prescription drugs (including, e.g., OTC medications, vaccines, surgical procedures, alternative medicine, even changed lifestyles)

Increased competition is a strong driver of LCM. New indications and more differentiated formulations may help to differentiate a drug from other offerings in the same drug class or for the same disease, and can be employed proactively and/or reactively to attain or maintain competitive advantage. And after patent expiry, patented line extensions may enable a brand to retain a higher share of the genericized market when facing intramolecular competition.

1.6 EARLIER GENERICIZATION

There are several different causes of earlier genericization, but the net result is the same: brands lose their exclusivity earlier in the life cycle.

The main reason for earlier genericization is that generic companies are now large, rich, confident, and experienced enough to enter into patent litigation with branded drug companies, or even to launch their generic product at risk, when they believe a patent to be invalid.

In the United States, the Hatch–Waxman legislation actually offers generic companies an incentive to invalidate drug patents, by providing 180-day marketing coexclusivity with the brand to the generic company that files the first Abbreviated New Drug Application (ANDA).

We will be looking at the Hatch–Waxman legislation in the United States later in the book, but another of its immediate effects when it was first passed back in 1985 was to establish the so-called safe harbor which allowed generic companies to conduct bioequivalence studies with patented drugs before patent expiry, thus enabling them to launch their generics on the very day that the patent expired instead of some months afterward.

A more recent event that may dramatically weaken some patents and thus further encourage earlier generic entry to the market is the 2007 ruling in the *KSR versus Teleflex* case. We will look at this landmark decision in depth later, but the bottom line is that the ruling has raised the bar on what can be considered a “nonobvious” invention. Some new formulations and fixed-dose combinations that were considered innovative and therefore granted a patent in the past will find it more difficult to obtain and maintain patent protection in the future.

There is no excuse for companies that do not prepare their brands for basic patent expiry. After all, on the day the patent is granted, a company knows exactly when the patent will expire two decades into the future. Planning for patent invalidation or at-risk generic launches is much more difficult, as the time point of the generic entry is not known in advance.

LCM strategies for maximizing the period of exclusivity, or at least limiting the impact of early genericization, include the construction of complex combinations of patents which are hard to invalidate and slight modifications of the drug substance which effectively create a new brand franchise. Again, we will be looking at this in considerable detail later in the book.

In practice, it is getting more difficult to obtain secondary patents, and many that are granted are very vulnerable to circumnavigation or challenge by generic companies. There is thus a large question mark against the sustainability of many LCM strategies which are based on the robustness of secondary patents.

1.7 FASTER SALES EROSION FOLLOWING PATENT EXPIRY

A separate but related issue is the rate at which generics gain market share from the brand once the patent has expired or has been invalidated. Clearly, generic substitution is an effective means of reducing health-care spending on drugs, as in many markets, generics cost only a tiny fraction of the brand price.

As was the case with pricing and reimbursement, different countries have chosen different mechanisms to promote generic substitution. As an example, in the United Kingdom and Spain, pharmacists are allowed to substitute

Country	Pro-Generic reforms
United States	<ul style="list-style-type: none"> • ANDA reviews to continue in parallel with the processing of Citizen's Petition to minimize the delay of Gx marketing approval
United Kingdom	<ul style="list-style-type: none"> • The Department of Health is considering imposing mandatory generic substitution by pharmacists
Germany	<ul style="list-style-type: none"> • Although not a reform, a precedent set in the approval of a near generic version of Plavix indicates opportunity for the future approval of other near generics with minor differences in composition compared to the originator • Germany is the largest Gx market in the EU and has had a range of pro-Gx legislature
France	<ul style="list-style-type: none"> • Price cuts for both branded and Gx drugs
Spain	<ul style="list-style-type: none"> • Price cuts of up to 25% on Gx drugs in July 2011 • Changes to reference pricing system as soon as the first Gx in a therapeutic group is added to the reimbursement list • Plans to make mandatory prescribing by active ingredient instead of brand name • A new Medicines Bill was passed that gave pharmacists the authority to carry out Gx substitution in 2006
Italy	<ul style="list-style-type: none"> • Price cuts of 12.5% on generic and off-patent drugs from June 2011 • Pharmacists were incentivized to dispense Gx by receiving 8% of the margin on the generic drug in 2009
Japan	<ul style="list-style-type: none"> • Incentives for physicians prescribing Gx drugs • Implementation of guidance for biosimilars' approval in March 2009

FIGURE 1.7. Health-care reforms in the 7MM aimed at increasing the use of generics. Sources: www.scripintelligence.com; Datamonitor pharmaceutical market overview reports.

brands prescribed by the physician with a generic. In the United Kingdom, substitution is encouraged by requiring physicians to prescribe drugs by the International Nonproprietary Name (INN) instead of by brand name, and pharmacists are incentivized to dispense generics. In Spain, physicians receive a lump sum payment if they reach annual generic subscribing targets. Figure 1.7 shows an overview of some of the methods used to encourage generic approvals and generic usage in seven top pharmaceutical markets.

The introduction of an improved formulation of the original brand, protected by a secondary patent, has historically been one of the most successful strategies for maintaining postpatent sales, and we will look at several examples of this strategy later in the book. The new formulation is introduced a year or two before the basic patent expires, the sales force persuades physicians to prescribe the new formulation, and by the time the generic arrives in the old formulation, the market has moved on to the new formulation so that there are few sales remaining for the generic to cannibalize.

But here as well the LCM environment is getting tougher. The new formulation must overcome a whole series of barriers before it can be commercially successful, and we will be looking at this later in the book. The barriers include:

- As mentioned earlier, will the secondary patent be granted, or is it too “obvious”?
- Is it robust? Can it withstand challenge?
- Can it be circumvented, that is, can another formulation with the same advantages be made without infringing the patent?
- Is the new formulation differentiated enough to get a premium price?
- After basic patent expiry, will it be reimbursed, listed, prescribed, and dispensed at that price, or will prescription sales move to the generics?

The combined effect of less new drug approvals and faster sales erosion by generics is demonstrated by the following figures. Murray Aitken, an IMS vice president, was quoted by *Forbes* in May 2010 as stating that 81% of U.S. drug sales in 2009 were for medicines where a generic was already available, compared to 61% in 2003; in 2003, 84% of patients prescribed a drug where a generic was available would get the generic, compared with 91% in 2009—put another way, in 2009 the brand was only retaining 9% of sales following genericization in 2009 compared with 16% in 2003, a drop in market share of 44%. With the one exception of Lipitor (which was due to go generic in 2011), the most prescribed drugs in the United States were now all generics (*Forbes*, “The death of the blockbuster,” May 28, 2010).

1.8 POOR IMAGE OF BRANDED DRUG INDUSTRY

This is a controversial area, but as it is a key aspect of the problems that the branded drug industry are facing, and has a considerable impact on LCM strategies, it does need addressing here.

Once upon a time, around 25 years ago, branded drugs were regarded as one of the most innovative, socially aware, and ethical of all industries. This started to change as the profitability of branded drug companies rose to levels that were far above the average for other manufacturing industries, while at the same time innovation started to flag. Gradually, the perception gained strength that branded companies, and especially “Big Pharma,” were not only exploiting sick people to line their own pockets, but were failing to even provide worthwhile new drugs that might at least partly justify this behavior. A Harris Interactive poll in 2010 showed the extent of the problem, comparing how much trust consumers have in different industries, highlighted in Figure 1.8. The results of these Harris polls are always rather depressing, but at least drug companies have improved by 1% since the last report in 2008. Looked at from the other side, however, it still means that nearly 90% of the U.S. public consider the pharmaceutical industry to be untrustworthy and dishonest.

What on earth are the reasons for this change in perception? Most of us in the industry are still proud of our contribution to the reduction of human pain

Perceptions of industry being honest and trustworthy among U.S. adults, 2010

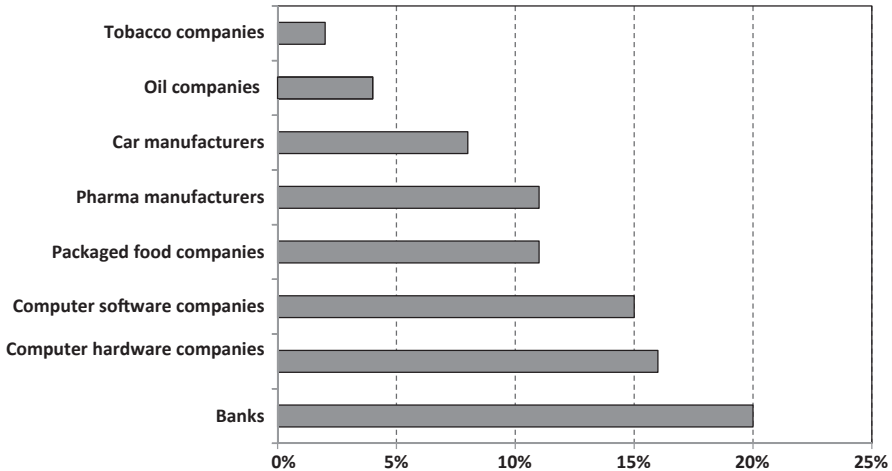


FIGURE 1.8. Public image of the pharmaceutical industry. *Source:* www.harrisinteractive.com.

and suffering, but that is not the way we look from outside of the industry. There are several reasons, and we have already touched on some of them.

1.8.1 Prosperity of the Branded Drug Industry

In many countries, society has the perception that good health—and therefore also health care—are basic human rights almost on the same level as clean drinking water and free oxygen to breathe. While society accepts that richer members of society are likely to enjoy better food, bigger houses, faster cars, and more elegant clothing, it seems wrong that they should also have better disease prevention, more effective therapies when they are ill, and consequently, less disability and a longer life expectancy. As long as poorer countries and weaker members of society do not enjoy the same benefits of good health care as the better-off citizens of the developed countries, it therefore seems to many to be vaguely indecent that pharmaceutical companies should reap huge profits in creating and selling drugs that are unaffordable for a large portion of the population.

And the branded drug industry is indeed very profitable. According to *Fortune* magazine, the profits of the U.S. pharmaceutical industry as a percentage of sales stood at 19% in 2008. Manufacturers of network and communications equipment were slightly more profitable at 20%, and medical equipment manufacturers not far behind at 16%, but all other manufacturing industries stood at 10% or less (*Fortune*, May 4, 2009). In this context, it is worth remembering that the profitability of retail pharmacies, pharmacy benefit managers

(PBMs), and payers is less than 5%. Executive compensation, which has been strongly criticized for the financial sector during the recent downturn, seems to be less of an issue for the drug industry in most countries. But there is sometimes criticism of chief executive compensation, for example, recently in the cases of Bill Weldon at J&J and Dan Vasella at Novartis.

The pharmaceutical industry is in a particularly vulnerable position when it comes to defending what is sometimes seen as its financial excesses, as it is in continual negotiation with governments and third-party payers regarding prices and reimbursement.

1.8.2 Lack of Innovation

We have already looked at this issue. In the 10 years from 1987–1997, the branded drug industry introduced important new classes of medicine to world markets. Examples include serotonin-specific reuptake inhibitors (SSRIs) for depression, statins for lowering cholesterol, proton pump inhibitors (PPIs) for gastric ulcers, ARBs for hypertension, and highly active antiretroviral treatment (HAART) therapy for AIDS. Since then, apart from Gleevec®, which is effective in a number of rare cancers, very few major new drug classes have launched, with one of these being the COX-2 inhibitors, which have since had to be withdrawn for safety reasons. As long as the branded drug industry was producing important new drugs, there was a broad acceptance that the companies should be allowed to earn good profits. Once innovation flags, but profits remain high, the potential for criticism obviously rises.

1.8.3 Marketing Spend and Tactics

While Big Pharma has repeatedly stated that it needs high profit margins to finance its expensive and high risk research efforts to find new drugs, critics have been quick to point out that the R&D spend of these companies is less than half of their sales and marketing spend. Indeed, a report by two University of York researchers in 2008 revealed that the U.S. pharmaceutical industry spent 24.4% of its sales dollars just on promotion compared with 13.4% on R&D (Gagnon and Lexchin. 2008. “The cost of pushing pills: A new estimate of pharmaceutical promotion expenditures in the United States,” *PLoS Medicine*). Some specific marketing practices have also come under heavy fire. In 2009, following a 4-year investigation, Pfizer was fined a total of US\$2.3 billion for illegally promoting Bextra and other brands. The illegal marketing practices included paying physicians, resort trips, and kickbacks for prescribing Pfizer drugs for off-label indications; Pfizer had already been fined a total of US\$500 million over illegal marketing since 2002 even before the 2009 judgment.

Industry critics point out that the affordability of even large fines is a problem regulators face in deterring such activity. In the case of drugs generat-

ing billions of dollars in sales every year, even fines of US\$1 or US\$2 billion do not offset the money to be made from off-label marketing.

Some controversial direct-to-consumer advertising campaigns have also come under fire, and lawsuits have targeted questionable pricing to state Medicaid programs. In just one recent year, the U.S. Justice Department had 150 cases on its docket of alleged fraud by pharmaceutical companies (*FORC Journal*, 2007, Vol. 18, Edition 3, Fall).

The less brands a company has on the market, and the less differentiated these brands are, the more necessary it becomes to utilize all possible marketing strategies to stimulate sales.

1.8.4 Safety Issues

Again, we have already considered this. But from the public image perspective, the main issue has not always been the safety issues per se, but rather how the pharmaceutical industry is perceived to have handled them. The popular press abounds with articles stating that pharmaceutical companies hide negative results from the public and continue to sell drugs that they know to be dangerous. One recent example in the *New York Times* of June 13, 2010 related to Avandia.

However, the most prominent recent example of concealment of negative results related to Merck's Vioxx. Hailed initially as a breakthrough pain therapy, Vioxx was withdrawn from the market in late 2004 after results from a clinical trial indicated an increased risk of heart attacks in patients taking the drug. Shortly afterward, *The Lancet* published a meta-analysis of available studies which indicated that "the unacceptable cardiovascular risks of Vioxx were evident as early as 2000" (*The Lancet*, 2004, Vol. 364, No. 9450, pp. 1995–1996).

In May, 2008, Merck was found guilty of using deceptive marketing tactics to promote Vioxx, and 30 states will split the resulting US\$58 million settlement. At that time, the amount was the largest multistate settlement against a pharmaceutical company.

Legal cases involving the families of patients who were prescribed Vioxx and who died of heart attacks continued to appear in the press, and in 2007 Merck announced that it would fund a US\$4.85 billion settlement expected to resolve roughly 50,000 lawsuits (Merck Press Statement, November 9, 2007).

Still the controversy continued, and in 2009, the U.S. Circuit Court of Appeals agreed to allow a class-action securities lawsuit connected to what Associated Press has described as "tens of billions of dollars in shareholder value" that plummeted when Vioxx was withdrawn from the market (reported in *WSJ*, April 27, 2010). Investors are accusing Merck of omission of critical information and releasing misleading information on Vioxx's risks.

Merck's defense was that its investors should have been aware, based on information in the public domain, that problems could have been existing with Vioxx, citing a U.S. FDA warning issued to the company regarding Vioxx in late 2001.

Merck was also relying on a 2000 study, the Vigor trial, which compared Vioxx to naproxen. In this trial, Vioxx patients had a fivefold increased risk for heart attacks (*New England Journal of Medicine*, 2000; 343:1520–1528). Merck maintained in a press statement that this should have provided investors with adequate warning of potential problems with Vioxx. But Merck had long argued in the opposite direction, against the interpretation that Vioxx was causing the heart attacks. Merck had maintained that naproxen was in fact preventing them. The investors' lawyer, David C. Frederick, stated that "It would be the height of irony that for Merck's success in concealing its fraud through the scientific uncertainty that was occurring with the naproxen hypothesis, that it would have this suit thrown out on statute of limitations grounds and never face the day in court that the investors here expect and deserve" (reported in *Washington Times*, December 1, 2009).

And to add to Merck's woes, in 2009, Scott S. Reuben, former chief of acute pain at Baystate Medical Center, admitted that data for 21 studies he had authored had been fabricated in order to enhance the analgesic effects of the drugs. It was pointed out that Dr. Reuben was also a former paid spokesperson for Pfizer, which owns the original Vioxx patent (*WSJ*, March 11, 2009).

Perhaps Merck could not have done more to avoid the Vioxx safety issue and subsequent withdrawal; after all, it is logical and acceptable that side effects with a low incidence will only appear after a drug has been approved for usage in broad patient populations. But, in retrospect, Merck would no doubt have liked to handle certain aspects of the case differently.

One key learning from the Vioxx case is how ready public opinion is to believe the worst of a large pharmaceutical company, even that the company is knowingly selling a drug which kills patients. As such, the Vioxx case is a prime example of just how far trust in the pharmaceutical industry has deteriorated.

1.8.5 Keeping Generics Off the Market

Some of the measures that branded drug companies employ to maintain exclusivity and keep generics off the market have met with considerable public and official criticism in recent years. There is growing concern that the majority of patents taken out by the pharmaceutical industry protect minor and often obvious "improvements" in existing drugs, and that they only serve to delay or prevent cheaper generic medicines reaching the market rather than providing any tangible benefit for patients.

On July 8, 2009, announcing the adoption of the European Commission Final Report on its competition inquiry into the pharmaceutical sector, Neelie Kroes, the European Commissioner for Competition, stated that "The inquiry has told us what is wrong with the sector, and now it is time to act. When it comes to generic entry, every week and month of delay costs money to patients and taxpayers. We will not hesitate to apply the antitrust rules where such delays result from anticompetitive practices. The first antitrust investigations

are already under way, and regulatory adjustments are expected to follow dealing with a range of problems in the sector.” The Final Report stated that “The inquiry concentrates on those practices which companies may use to block or delay generic competition as well as to block or delay the development of competing originator products.”

In February 2009, the U.S. Federal Trade Commission (FTC) sued the branded drug company Solvay and the two generic companies Watson and Par Pharmaceuticals for attempting to delay generic competition to Solvay’s branded testosterone-replacement drug AndroGel®, a prescription pharmaceutical with annual sales of more than US\$400 million (FTC press release, February 2, 2009). According to the Commission’s complaint, Watson and Par each sought regulatory approval from the FDA to market generic versions of AndroGel. In their FDA filings, both companies certified that their products did not infringe the only patent Solvay had relating to AndroGel, and also that the patent was invalid. The complaint charged that Solvay subsequently agreed to pay the generic companies to abandon their patent challenges and agree not to bring a generic AndroGel product to market until 2015.

“At a time of escalating health care costs, these unlawful agreements deny patients the benefit of competition between branded and generic pharmaceuticals and ultimately cost consumers hundreds of millions of dollars a year,” said Acting FTC Bureau of Competition Director David P. Wales.

In his separate statement, FTC Commissioner Leibowitz stated, “This is yet another example of pharmaceutical companies turning competition on its head. . . . Congress enacted the landmark 1984 Hatch–Waxman Act to encourage early generic entry and save consumers money, but these anticompetitive deals threaten to destroy that benefit and make crucial portions of the Hatch–Waxman Act extinct in all but name.”

The main focus of LLCM (late-stage lifecycle management) in branded drug companies is, indeed, to utilize all available measures to maintain brand exclusivity for as long as is legally possible. Every loophole in the pertinent legislation will be taken advantage of as the financial benefits of blocking generic entry are so gigantic.

Among our case histories in this book, we will be looking more closely at a pivotal case of LLCM, that of AstraZeneca’s Nexium®. This was commercially very successful, but also encapsulated several controversial elements of how a major branded drug company with a poor pipeline managed to rejuvenate an old brand to compensate for a lack of NMEs. It prompted the former editor of the influential *New England Journal of Medicine*, Marcia Angell, to make the much-quoted statement in 2004 that the story of Nexium and drugs like it is proof that the pharmaceutical industry is “now primarily a marketing machine to sell drugs of dubious benefit” (Marcia Angell. 2005. *The Truth About the Drug Companies: How They Deceive Us and What to Do About It*, Random House).

Summarizing all that we have written so far in this first chapter, it can be categorically stated that the branded drug industry is facing more challenges

Top 10 pharma sales growth forecast 2013–2014

Rank	Company	% growth
1	Pfizer	–1.7
2	Novartis	2.9
3	GSK	6.2
4	Merck & Co.	–0.6
5	Roche	1.9
6	Sanofi	2.5
7	AstraZeneca	1.4
8	Johnson & Johnson	–0.5
9	Abbott	–3.1
10	Eli Lilly	–9.4

FIGURE 1.9. Growth forecasts. *Source:* Datamonitor PharmaVitae Explorer.

today than at any time in its recent history. Empty pipelines, higher development costs, lower prices, increased competition, and shorter brand life cycles constitute such a powerful combination of threats that many industry observers are asking whether we are currently seeing the beginning of the end of Big Pharma as we know it. In January 2010, on a single day, AstraZeneca announced it will cut 8,000 jobs worldwide, and GSK announced that 12,000 positions will be eliminated by 2014. And then in July 2010, Merck announced following its merger with Schering Plough in the previous year that 15% of its workforce, or 15,000 persons, would be put out of work over the following 2 years. It is in this environment that interest in LCM blooms, as desperate companies try to squeeze more sales and profits out of their diminishing portfolio of brand assets.

Industry analysts are almost united in their projections that the branded drug industry will be unable to maintain the growth and profit levels that it has taken for granted for the last quarter century. As an illustration of what is expected, Figure 1.9 shows recent estimates for top-line growth for the leading companies from 2013–2014.

1.9 DIVERSIFICATION

As the discovery of new drugs becomes increasingly difficult, some branded drug companies are looking to spread risk by diversifying their businesses away from an overdependence on prescription drugs. Whether to follow this trend, and how widely to diversify away from the core business, is a quandary

faced by many large and mid-sized brand companies, and there is no consensus yet on what the best approach might be. The very broadly diversified chemical/pharmaceutical company seems to be a thing of the past. Historically, the drug industry grew out of the chemical industry in many cases, and was just one part of a widely diversified business portfolio based on chemistry. Just to take one of many examples, before its merger with Sandoz to form Novartis in the late 1990s, Ciba Geigy's business portfolio consisted of industrial chemicals (dyes for textiles, paper and leather, pigments for paints and plastics), precision balances, contact lenses, contact lens disinfectant solutions, plastics, health-care products (pharmaceuticals, OTC, and diagnostics), and agricultural chemicals (herbicides and pesticides). Later, companies tended to narrow their focus, with major players like Pfizer, Merck, and Roche concentrating their efforts on prescription drugs. Companies like Johnson & Johnson (J&J), with a broad business portfolio within what could loosely be defined as "health care," were rather unfashionable. Today, J&J looks almost like a role model as Big Pharma prescription drug companies spread out into adjacent areas like OTC, generics, diagnostics, medical devices, and eye care.

In the context of our book it is worth bearing in mind that this diversification of business interests can open up new in-house opportunities for LCM, both for increasing and defending prescription brand revenues.

The most obvious example of diversification supporting LCM is where a brand company sets up its own generics division, working on the time-honored principle of if you can't beat 'em, join 'em. The best industry example of diversification into generics is Novartis. Novartis's generics arm, Sandoz, is the second biggest generics company in the world behind Teva. Generics have a long history at Novartis, as both of the predecessor companies had generic businesses even before their 1996 merger. Ciba Geigy had sold generics under the Servipharma, Geneva, and Multipharma brands starting in the 1970s, and Sandoz had had a generics division, Biochemie, since the 1960s, adding the Azupharma acquisition shortly before the merger with Ciba Geigy. Within Novartis, all of these generic companies were grouped together under the resurrected Sandoz company name in 2003, and the subsequent acquisitions of BASF Generics, Lek, Hexal, and Eon enabled Sandoz to climb to its current position among the industry leaders.

Novartis is, of course, not alone in its endeavors to diversify into generics. In its 2009 Annual Report, Pfizer wrote "Pfizer is a growing force in the rapidly expanding but highly contested generics marketplace. While we have a huge generics catalog of our own, we recently entered into major licensing agreements with three India-based pharmaceutical companies, Claris Lifesciences, Aurobindo Pharma, and Strides Arcolab. These agreements will bring hundreds of high quality generic medicines to underserved populations around the world and add numerous products to Pfizer's portfolio of established brands in key markets." Pfizer tried to buy Germany's Ratiopharm in early 2010 but was outbid by Teva. Speculation through 2010 suggested that Pfizer's next target for strengthening its generics interests might be Stada, but that

deal never materialized. Instead, in its Q4/2010 earnings call, Pfizer had to announce that the sales of its Greenstone generics unit had slumped by 14%.

Other Big Pharmas were also actively building up their stakes in generics. In 2009, Sanofi-Aventis acquired Zentiva, a branded generics group with products tailored to the Eastern and Central European markets, as well as Kendrick, one of Mexico's leading generics manufacturers, and Medley, a leading generics company in Brazil. Then in May 2010, Sanofi-Aventis strengthened its position in the emerging Japanese generics market by launching a joint venture with Nichi-Iko K.K., the leader and fastest growing generics company in Japan. The joint venture is 51% owned by Sanofi-Aventis.

GSK increased its shareholding in Aspen during 2009; Aspen is a major supplier of generics and branded generics in South Africa and also exports to some markets. GSK also acquired BMS's mature products business in Egypt during 2009 and, in 2010, added Argentina's Laboratorios Phoenix.

AstraZeneca, one of the Big Pharmas which has suffered most from patent expiries of its leading drugs in recent years, stated in its 2009 Annual Report that it intends to selectively supplement its Emerging Markets portfolio with branded generic products sourced externally and marketed under the AstraZeneca brand, and in 2010 announced three generics pacts with Aurobindo, Torrent, and Intas.

Will this recent interest of Big Pharma in the generics industry prove to be successful? It is something of a credibility tightrope walk for a company active in both the branded and generic industries to on the one hand aggressively defend its own intellectual property while at the same time trying to find loopholes in the intellectual property of its competitors. Also, it is difficult to house the two different mind-sets, business models and company structures under one corporate umbrella, as we will be discussing later in the book. Not all Big Pharmas have jumped onto the bandwagon. Large companies that have, so far at least, distanced themselves from building their own generic businesses include Roche and BMS.

Once exclusivity has been lost, most large branded drug companies have to continue to invest in their old brands by managing them in units with names like "established medicines" or "mature products." The situation might be different if industry pipelines were full, but in the current situation, companies cannot afford to give up on their patent-expired brands even after exclusivity has been lost. Again, we will be looking at the options for LCM of genericized brands in more detail later.

Another common diversification strategy for Big Pharma, and one that is much older than the current trend to move into generics, is the maintenance of an OTC business unit. There are several reasons why a brand company in the prescription drugs sector would wish to be involved in the OTC sector as well:

- Shifting prescription brands to OTC status as part of brand LCM, either as an expansion strategy in mid-life cycle or as a way of escaping from

generic competition following patent expiry. We will be looking at this in detail later in the book.

- Benefiting from the trend for third-party health-care cost containment by moving more medicines to OTC status.
- Gaining better understanding of the self-pay prescription/OTC hybrid model prevalent in many emerging markets.
- Cycling prescription drug marketers through the OTC business to give them a better understanding of direct-to-consumer (DTC) advertising and marketing.
- Getting more public recognition for the company name.

Other business diversification strategies which can provide brand LCM opportunities and are therefore relevant to the subject of this book include moves into animal health, medical devices, diagnostics, and drug delivery. Gaining access to proprietary medical devices and drug delivery systems can be a valuable strategy for both expansion and defense of a brand.

Two common diversification strategies that do not directly benefit pharmaceutical brand LCM are medical nutrition and vaccines.

The world champion at diversification is, and have been for many years, J&J. Their business portfolio includes such brand names as Johnson's Baby Care®, Piz Buin®, Band Aid®, Listerine®, Carefree®, o.b.®, Tylenol®, Pepcid®, Benecol®, Acuvue® Contact Lenses, DePuy, Cordis, Lifescan, Ortho®, Ethicon®, Duragesic®, Risperdal®, Remicade®, Janssen, Centocor, and McNeil. In April 2011, J&J announced that they were acquiring for US\$21 billion Synthes, a leading manufacturer of instruments, implants and biomaterials for the surgical fixation, correction, and regeneration of the human skeleton and its soft tissues.

Another diversification dimension which is very relevant for brand LCM is geographical. Most brand companies are intensifying their efforts in emerging markets, especially the BRICT countries (Brazil, Russia, India, China, and Turkey) where intellectual property, pricing, and reimbursement are treated differently compared to the traditional top-priority markets in North America, Western Europe, and Japan. In one recent example, in May 2010, Abbott announced it had bought India's Piramal for nearly US\$4 billion to gain the number 1 position in the Indian pharmaceutical market.

The key question for diversification, however, remains—is the goal to de-risk the business through spreading bets across a number of different sectors or to create synergies that allow each different operation to increase the value of its neighbors? For many companies, diversification is now simply a necessity to cope with a blended reality of the future of the pharmaceutical industry. As growth markets such as India and China become more important, the boundaries between prescription drugs, generics, and consumer health care will become even more blurred, and it will be those companies that can adapt to the needs of different markets that will succeed.