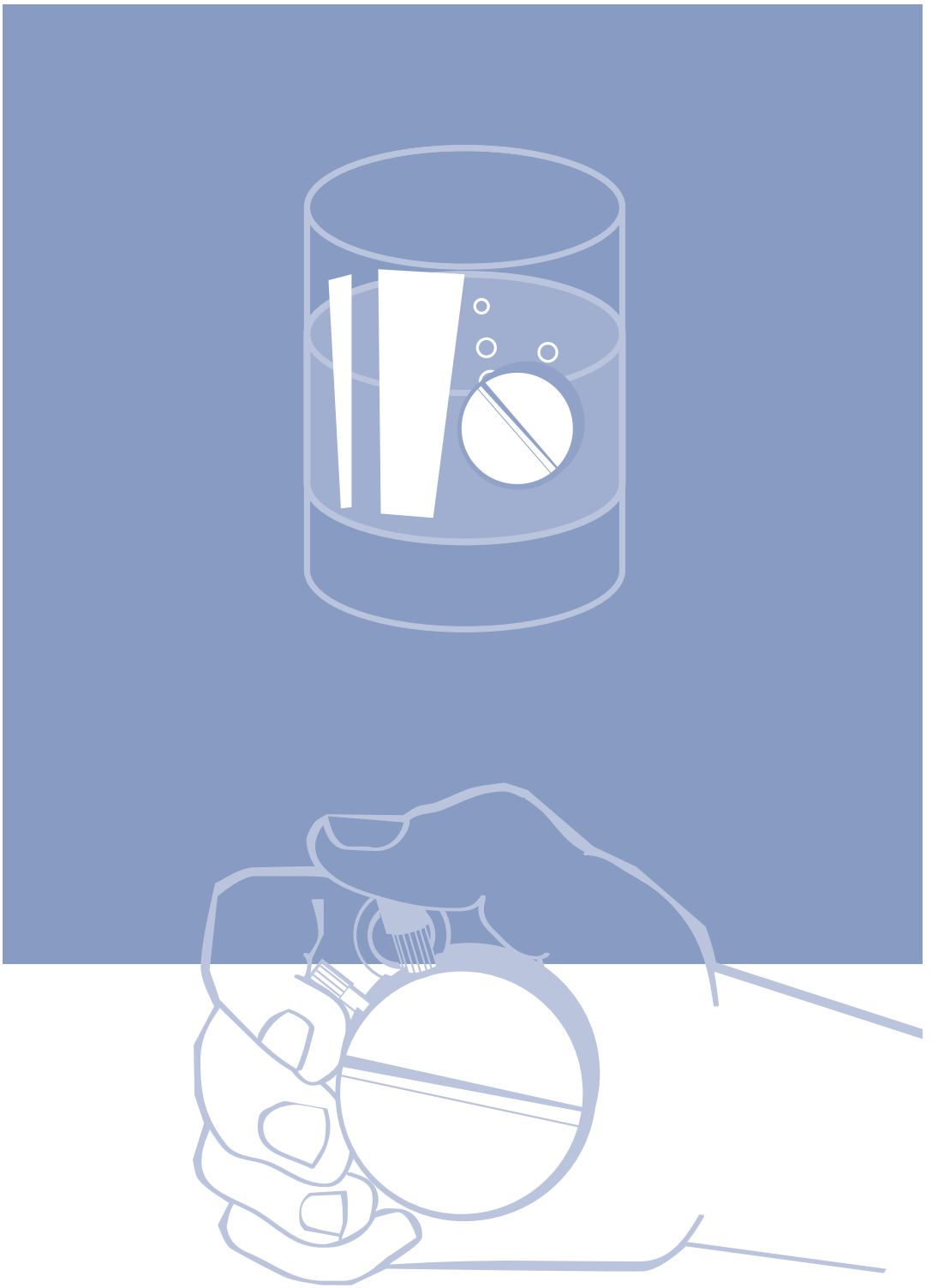


Mid-Life Crisis: New Challenges in Pharmaceutical Life-Cycle Management

Francois Deneux, Robert L. Kane, Rolf Lundh, Albert Schaper, Frédéric Thomas

The pharmaceutical industry has been a fast-growing sector for many decades. Historically, this success was built on the optimum use of a unique business model based on innovation and particularly on the development of patented new chemical entities. Public authorities have supported such innovation by allowing companies to achieve market exclusivity through patent protection. The success of this industry is now being challenged. Many big products have lost or will soon lose their patent protection and generic producers are taking important shares in the market for these products. The authors offer insights into the situation of the pharmaceutical industry and where companies need to evolve if they want to be around tomorrow.

For many decades, the pharmaceutical industry has been a fast-growing sector generating high margins. The strength of its performance has been recognised by financial markets, which have historically given pharmaceutical companies high valuations and considered them a safe investment.

Historically, this success has been built on the optimum use of a unique business model based on innovation and particularly on the development of patented new chemical entities. Public authorities have supported such innovation, which requires large-scale investment, by allowing companies to achieve market exclusivity through patent protection. Basically, patents establish temporary monopolies that allow pharmaceutical companies to sell their products at a high price. The price of an innovative product is based on its therapeutic value (its clinical benefit and the nature of the disease it is designed to combat) more than on costs or on existing market prices (except for commodity products and generics). In this market, even when a monopoly moves toward an oligopoly with the entry of "me-too" products, the competition rules do not fundamentally change: competition is over prescriptions, which generate sales volumes, while competition on prices remains very low.

The success of this industry is now being challenged, largely because the industry does not seem to be able to renew its product portfolio. Many big products have lost or will soon lose their patent protection and generic producers are taking important shares in the market for these products. Moreover, for demographic reasons customers are increasingly concerned with getting value for money, resulting in cost-measurement activities that are putting pressure on prices, particularly in Europe. Consequently, the confidence of financial markets in pharmaceuticals is declining.

The industry used to have a very high level of confidence in its business model, which is based exclusively on inno-

vation, intellectual property and high prices. Its success in the past has created certainties, especially concerning this business model, that may handicap its ability to adapt to market changes. Meanwhile, evolutionary forces are introducing new issues that the industry will have to deal with in the coming years, such as:

- Is it possible for the pharmaceutical industry to continue to develop a unique business model based on innovation and intellectual property?
- Is the business model the right one for all the pharmaceutical companies?
- Do pharmaceutical companies have to accept the development and reinforcement of generics producers? Is it possible to allow them to take a growing share of the market?
- Will societies in the future continue to accept the (still) high profit margins of the pharmaceutical industry?

The Historical Model: Life-Cycle Management of Pharmaceutical Products

When analysing the past growth of the main pharmaceutical companies or their present turnover, the predominance of a very limited number of products is striking. The worldwide success of these companies has been based mainly on the sales of fewer than 10 products and very often of fewer than five.

Exhibit 1 **Sales Rank and Turnover**

Rank by audit sales	Corporation	Number of Blockbusters	Blockbuster sales/ Ethical sales (%)
1	Pfizer	8	79.8
2	GlaxoSmithKline	9	50.7
3	Merck & Co.	5	63.0
4	Johnson & Johnson	4	56.3
5	AstraZeneca	2	47.8

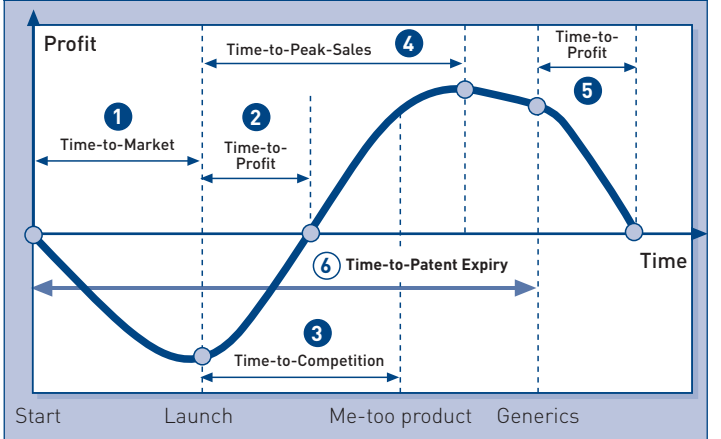
Source: Arthur D Little analysis

The number of important products is small. That's why we consider the analysis of life-cycle management of phar-

maceutical products the best way to understand the business model of the industry, how pharmaceutical companies have optimised it and the new issues they are now facing.

The business model of the pharmaceutical industry is based on intellectual property and patents. When a pharmaceutical company files a product patent, during the research phase, it starts the period of protection and determines the date of the potential entry of generic rivals into the market. At patent publication, a large part of the content of its research is explained to the scientific community and therefore to other pharmaceutical companies. From the beginning of the development of a pharmaceutical product, the company is racing against the (patent) clock more than against competition. Therefore the life-cycle management of pharmaceutical products is based on mastering lead times.

Exhibit 2 **Key Variables Life Cycle of Pharmaceutical Products**



Source: Arthur D Little analysis

There are six key variables to be considered in effective life-cycle management:

- **Time-to-market** covers the pre-clinical phase (trials on animals – when possible – to determine the efficiency and toxicology of the product), clinical trials (phases 1 to 3 on human beings), regulatory requirements (filing, assessment and approval) and, in some countries, pricing negotiation. This lead time is critical because of its length (usually between seven and 12 years, com-

pared to a patent protection of 20 years), and because it determines the date of the first sale and the duration of the product's commercial life before the patent expires. It is also important because there is a strong correlation between development duration and development costs.

- **Time-to-profit** is determined mostly by the costs of development, the costs of resources invested in the marketing of the product and the volume of sales. It is a good indicator of the efficiency of development and marketing and sales.

- **Time-to-competition** is a good indicator of a pharmaceutical company's research and development efficiency. It shows how much advance the company has had on its competitors. Depending on the type of product launched, it may be an advantage to be alone on the market when you introduce a new active mechanism or a disadvantage when you have to create and develop a new market.

- **Time-to-peak sales** is the main driver of sales volume before patent expiry, once the dates of product launch and patent expiry are determined.

- **Time-to-patent expiry** divides the product life cycle into two periods: before patent expiry, when oligopolistic rules of the game are applied, and after patent expiry, when new rules are initiated by the entry of generic manufacturers. Additional complexity can be introduced by intellectual property strategies that include the use of many patents (such as product-related, process-related or indication-related), making the date of the end of patent protection increasingly difficult to determine.

- **Time-to-collapse** determines the volume of sales made after patent expiry. This volume is important because it may generate significant profits, given that the costs of R&D and of gearing up for industrial production have been paid before patent expiry and the level of marketing investment is low on this type of product.

Optimising Life-Cycle Management Within the Historical Model

When managing the life cycle of its products, the pharmaceutical industry has given priority to three issues: reducing the time-to-market, reducing the time-to-peak sales and increasing the time-before-patent expiry.

In the 1980s, the industry focused strongly on shrinking the time-to-market. There were two main approaches: organising an overlap of the various development phases; and launching several studies in parallel at international level. These approaches induced a strong reduction in the time-to-market but increased development costs substantially, particularly in the case of failure.

Simultaneously, pharmaceutical companies increased the time-before-patent expiry with two approaches:

When managing the life cycle of its products, the pharmaceutical industry has given priority to three issues: reducing the time-to-market, reducing the time-to-peak sales and increasing the time-before-patent expiry

- Developing intellectual property based on production systems, new indications for the product and new drug-delivery systems - all aimed at postponing the date of the expiry of intellectual property protection;
- Legal strategies aiming at contesting the rights of potential new entrants (especially generics producers) to enter the market and compete.

As a result, the average duration of patent protection (the time between product launch and patent expiry) increased from 8.1 years in 1985 to 14.5 years in 1999. Another time-increasing factor was that, while 26 patents expired in 2001, the launches of 23 generic products were delayed until 2002.

In the 1990s, top-tier players focused on reducing the time-to-peak sales and tried to leverage their global presence. To reduce the time-to-peak sales and increase the level of peak sales, major pharmaceutical companies organised simultaneous launches in all major countries and invested tremendous amounts of money in marketing, especially pre-launch marketing. As a result, some companies launched products that reached a high level of sales at a speed never seen before. But, as a consequence,

the amount of investment needed for a launch increased significantly. The level of risk also increased, because a lot of money is invested before the company is sure either that the product will receive marketing authorisation or that the level of sales will meet the forecasts.

The "blockbuster approach" induces two effects: firstly, the big pharmaceutical companies concentrate their portfolios on a few major products and, secondly, all the big companies tend to focus their R&D on a small number of high-prevalence pathologies.

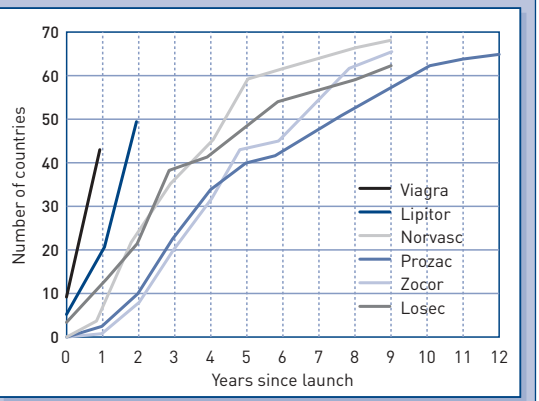
Because of the increase in the costs of development and launch, pharmaceutical companies tend to focus their resources on a few products that should become blockbusters (i.e achieve worldwide sales of over 1 billion USD).

The "blockbuster approach" remained the best way to optimise this business model during the1990s. It induced a decade of impressive development of the pharmaceutical industry, especially for the first-tier companies, which were able to mobilise and manage the important resources needed for the R&D and launch of "blockbuster" products.

Exhibit 3a **Blockbuster Approach: Global Reach of Top Brands 1998**

Challenge:

- To launch in more than 50 countries within 2 years
- Only large companies have the potential to benefit from a global presence and allocate enough sales force resource to roll-out the plan
- Even giants must co-promote to reach quick uptake before competition



Source: Arthur D Little analysis

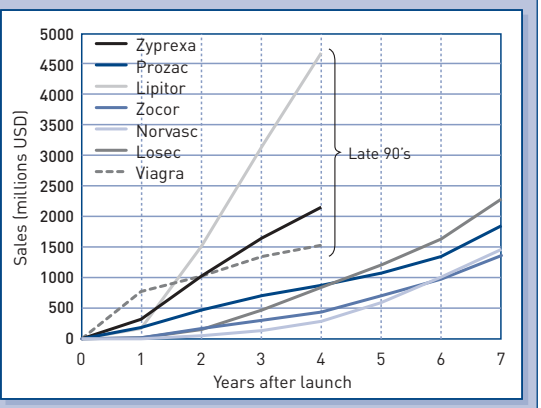
The "blockbusters approach" induces two effects: firstly, the big pharmaceutical companies concentrate their portfolios on a few major products and, secondly, all the big companies tend to focus their R&D on a small number of high-prevalence pathologies, some with important unmet medical needs, such as cancer, but also many with smaller unmet medical needs.

This approach to the life-cycle management of products is widely shared by most pharmaceutical companies and has

Exhibit 3b **Blockbuster Approach: Uptake of Mega-Brands**

Challenge:

- Recent product introductions achieved improved uptake
- Key drivers are:
  - Number of countries
  - Number of indications
  - Promotional Investments (# of reps)
  - Pre-launch activities



Source: ISM Health, Arthur D Little analysis

so far guaranteed the success of the industry. It is interesting to underline that most of the efforts of the pharmaceutical industry have been aimed at reinforcing this unique business model.

This choice is explained by two factors. Firstly, within the traditional business model products become medically obsolete before their patents expire, and generic products gain market share against declining products which have already been replaced by more efficient new molecular entities (NMEs). Secondly, generic producers try to replace a lot of "small" products by inducing more complexity and mobilising more resources compared to the potential turnover.

As a consequence, the attractiveness of the market segment of products after patent expiry has been low. Generic producers have not been very strong, pharmaceutical companies have been continuing to sell their products at a comparable price and time–to-collapse has been quite long.

The Changing Market: How New Developments are Threatening the Historical Business Model

A number of developments have created the present challenges to the pharmaceutical industry and its "pure" business model described above. The most important are:

- A decrease in the number of product launches, which correlates to a decrease in R&D's capacity to generate new products, an increase in the time-to-market and an increase in the costs of development and launching;
- A decrease in the time-to-competition;
- Strengthening of the generics producers due, firstly, to the fact that patent expiry now very often comes before product obsolescence and, secondly, due to the size of the products which have lost or will soon lose their patent protection.

The costs of developing a product have increased substantially (from 190 million USD in 1991 to 900 million in 2001). This level of investment limits the number of products that even the biggest pharmaceutical company can afford to develop simultaneously.

The first of these developments represents a decrease in pharmaceutical companies' innovation while they are investing ever-increasing amounts in R&D. Between 1996 and 2001, R&D investment in the USA increased from 12 to 24 billion USD, whereas the number of NMEs approved by the FDA decreased from 55 to 22.

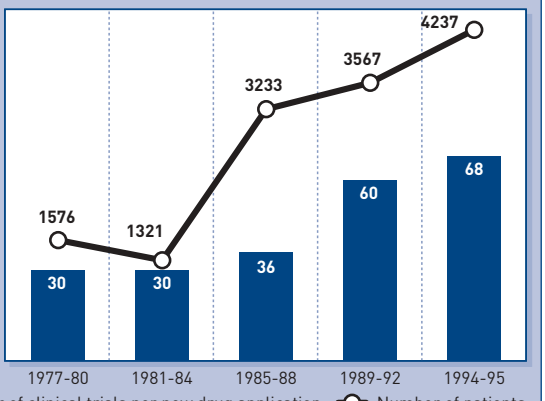
This trend correlates with a recent increase in the time-to-market (due to a lengthening of the development phase) despite a real increase in the efficiency of the development process. This additional lead time is mainly due to higher quality standards in clinical trials being set by public agencies (the FDA and EMEA) under the pressure of increasing risk-aversion among patients.

Exhibit 4 | **Time to Market and Cost Increase**

Trials and patient numbers per drug application

Challenge:

- To support NDA (New Drug Application) to FDA and EMEA, big pharma companies need to multiply clinical trials and patient cohorts
- Moreover, to gain sustainable competitive advantage, various indications are launched simultaneously



Source: ISM Health, Arthur D Little analysis

As a consequence, the costs of developing a product have increased substantially (from 190 million USD in 1991 to 900 million in 2001). This level of investment limits the number of products that even the biggest pharmaceutical company can afford to develop simultaneously.

At the same time, the costs of development limit the number of pharmaceutical

Medium-sized companies have to find new ways to develop because they do not have the resources to generate innovation and develop products at an international level.

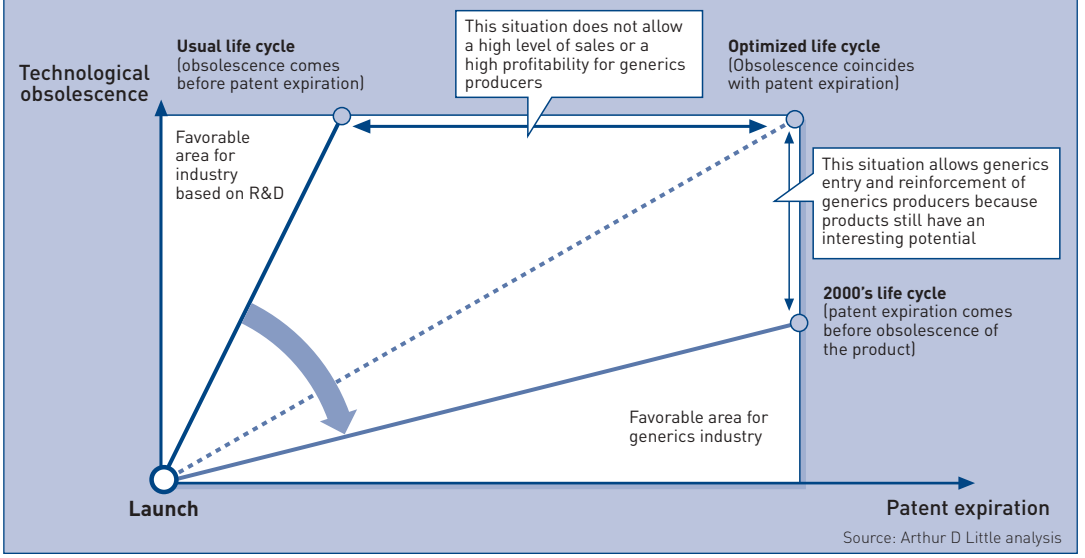
companies able to handle international development of a product. Medium-sized companies have to find new ways to develop because they do not have the resources to generate innovation and develop products at an international level.

The emphasis on developing blockbusters leads pharmaceutical companies to focus their R&D investments in the same therapeutic areas, those which hold the best prospects for the development of such products. Many companies are working simultaneously on similar technical approaches.

As a consequence, the second development is a decrease in the time-to-competition. Between 1970 and 2000, the period of time during which an innovative product was not in competition with another product decreased by four months every year. Today, a new product and its competitor are launched simultaneously or within a few months.

These developments have led to a major change in the market for pharmaceutical products: patents often expire before the products become medically obsolete.

Exhibit 5 | Impact of Life Cycle of Pharmaceutical Products



Source: Arthur D Little analysis

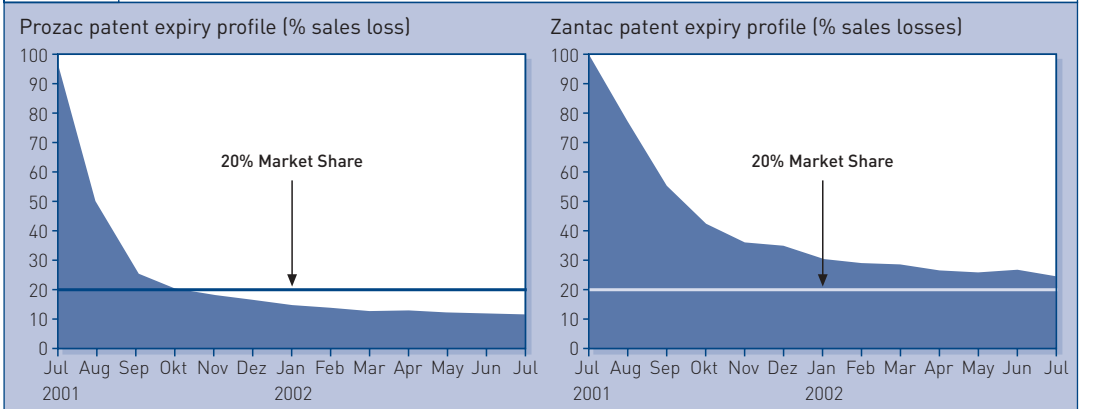
Pharmaceutical companies, even if they have a lot of assets at patent expiry, are unable to compete with generics producers.

The importance of this development is reinforced by the fact that the patents for many blockbusters have expired or will expire in the next few years. These products are feeding the growth of the market for "non-IP" pharmaceutical products (i.e those whose patents have expired).

The key success factors of this developing segment are different from those in the market for patented products. Pharmaceutical companies, even if they have a lot of assets at patent expiry, are unable to compete with generics producers. Prozac® is a good example of this new development of an important product losing its patent before it becomes medically obsolete. On August 2, 2001, the patent for Prozac® (fluoxetine) expired. The next day a generic of Prozac® hit the market, providing an opportunity to gauge the impact of competition with a generic product in this new environment.

The switch programmes were a success, with Express Scripts reporting an 81 percent mail service conversion rate one month after the generic became available. The swiftness and degree of generic substitution appeared to catch even Prozac's® manufacturer off guard. In an announcement in October that provided updated earnings guidance, Lilly CEO Stanley Taurel stated that "with nearly two months of Prozac® sales data available, the erosion in prescriptions is the most severe ever for a blockbuster product in our industry."

Exhibit 6 **Time to Collapse (US Market)**



Source: IMS data, Deutsche Bank

Because of the dynamism of this segment of the market, generic producers are becoming increasingly strong and increasingly difficult for the pharmaceutical companies to compete with in the generic market. Moreover, some of them are now able to develop aggressive legal strategies to contest the intellectual property of pharmaceutical companies.

In the US there is a six-month exclusivity period for the first generic producer receiving a marketing authorisation. This period is very important because the prices remain high and so do the margins, whereas later competition on price increases and margins decrease. As a consequence, some generic producers challenge pharmaceutical companies' patents years before the forecast date of expiry.

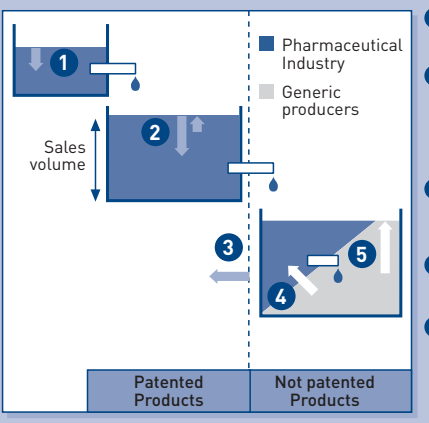
The approach to increase global sales by increasing price may be risky, because it increases the price differential between the products of the pharmaceutical industry and generics, which may encourage public authorities to give more support to generics.

The pharmaceutical industry is taking this situation far more seriously since November 2003, when the Food and Drug Administration, the US drug regulator, approved a version of Pfizer's blockbuster Norvasc (which had sales of USD 8.8 bn) produced by the Indian generics company Dr Reddys. Usually, generic producers aim at demonstrating that their product is the exact replica of the original, but Dr Reddys took a different approach. The company demonstrated that, when using the same basic molecule as Norvasc and a different salt to make the pills, it obtained the same therapeutic effects but did not infringe on Pfizer's patent. The US federal district court accepted that there was no patent infringement and the FDA approved the product.

Until now, the pharmaceutical industry has maintained and even increased its global sales by increasing the price of its products. This approach may be risky, because it increases the price differential between the products of the pharmaceutical industry and generics, which may encourage public authorities to give more support to generics.

Insights for the Executive: How Pharmaceutical Companies Can Adapt

Exhibit 7 Anticipated Trends in the Pharmaceutical Market



1. Decrease in the number of products developed and launched.
2. Decrease in the sales volumes correlated to decrease in the number of product launches, decrease in protection duration partly compensated by price increase.
3. Decrease in protection duration correlated to legal strategies of generic producers promoted by public organizations.
4. Decline in the time to collapse induced by the strength of generic producers.
5. Increase in the market share of not patented products correlated with the decrease of innovation/late technical obsolescence and a decrease in protection duration.

Source: Arthur D Little analysis

The business model developed by the pharmaceutical industry is very efficient when technological obsolescence comes before patent expiry, i.e. when innovation is strong enough. In these conditions, focusing on this unique business model based on innovation, intellectual property and high prices appears to be the best solution. However, when the rhythm of innovation declines, this business model cannot be maintained in the long run.

In recent years, the pharmaceutical industry has reinforced its marketing and sales efforts, especially by strongly increasing the number of sales reps. This investment has led to an important increase in the sales of products.

The pharmaceutical industry has to come back to fundamentals. The key driver of its business model is intellectual property. The industry thus needs to reconsider some aspects of its strategy in order to optimise this aspect. We consider that there are at least three issues concerned: the balance between R&D and marketing investments, the choice of therapeutic areas and the development of a "real" R&D strategy aiming more at intellectual property development than product development.

In recent years, the pharmaceutical industry has reinforced its marketing and sales efforts, especially by strongly increasing the number of sales reps. This investment has led to an important increase in the sales of products. Today, the pharmaceutical industry is investing between two and three times more in marketing and sales than in R&D. Even in bigger pharmaceutical companies (which

are the more innovative) R&D investment is between 14 and 18 percent of turnover, while the marketing and sales budget is around 35 percent. Innovation and intellectual property are a necessary condition of the business model of the pharmaceutical industry, while marketing and sales are "only" a way of optimising it. If the pharmaceutical industry wants to defend its business, it has to rethink the balance between these two budgets.

When considering the focus of the pharmaceutical industry in the past decade, one may get the feeling that the prevalence of pathology was more important than unmet medical needs. We think it is easier to launch a product when the unmet medical need is important. The industry should put more emphasis on unmet medical needs in its choices of strategic focus. This orientation could increase the industry's capacity for innovation in the coming years.

Intellectual property is at the root of the business model of the pharmaceutical industry. Very often the legal department takes care of this issue, and there are very few R&D or production programmes aiming only at defending and developing the intellectual property of a given company, in contrast to what happens in the biotech industry, for example. We consider that pharmaceutical companies should launch such programmes to more efficiently defend their business model.

Another issue that the pharmaceutical industry will have to consider is the relationship between size and business model. We have the feeling that most of the pharmaceutical companies today are trying to develop the same business model, but this business model should be adapted to the size of the company.

The first-tier companies could remain global players in R&D and marketing and sales because they are able to mobilise the necessary resources. The second-tier companies may remain global players in research and part of the development (up to phase 2), but they need to develop alliances to reinforce their capacity to handle the last phases of development – the registration phase and the international launch and marketing of products. These

companies should also think about less expensive ways to innovate and generate intellectual property, such as obtaining patents for combined product development, product optimisation and new drug delivery systems.

Smaller companies might only remain global during the research phase. There is also the question of their ability to maintain their technological level. The problem for these companies is that the proof of a concept is only established during clinical trials on humans. When proof has been given, these companies may settle agreements with bigger pharmaceutical companies to develop and value their projects. Such an approach corresponds to a new business model: it is why we think that these small companies have to be able to manage at least the beginning of clinical trials if they want to prove the value of their research. Otherwise they will have to merge to reach that level.

Finally, in view of the current evolution of the pharmaceutical market it is clear to us that the industry has to develop a second business model to deal with non-patented products, as this segment is developing and becoming more attractive. This is increasingly important because companies active in this field, particularly the generic producers, will try to attack the patented products segment and diminish it in size. Controlling the non-patented products segment appears to be a very good way of defending the patented segment.

Because the rules of competition are very different in the field of non-patented products, we believe that the pharmaceutical companies should develop specific entities to deal with products when they lose their patent protection.

François Deneux
... is a Partner in the Paris office of Arthur D. Little where he is responsible for the Healthcare Practice. He has fifteen years of experience in consulting. His main areas of interest are development strategies and organisational issues in the pharmaeutical and biotechnology industries. François Deneux holds an MBA from ESSEC and he is co-founder of two biotech companies.

Robert L. Kane
... is the Health Care Practice Leader in Arthur D. Little's UK management consulting practice. His areas of focus include business strategy, new product planning, technology commercialisation, e-health and valuation in health care markets. He has 20 years of consulting and industry experience in Europe and the U.S. with health care clients, financial institutions and technology companies. He has a BA in Microbiology from the University of Massachusetts (U.S.) and an MBA from Manchester Business School (U.K.).

Rolf Lundh
... is a Senior Manager in the Stockholm office of Arthur D.Little where he works for companies in the pharma, biotech and med tech sector. He has over 20 years experience in the pharmaceutical industry having held senior positions as a VP in large pharmaceutical companies both in Europe and the US. He holds an M.D. from the Karolinska Institute in Stockholm and is a licensed physician. He furthermore holds a Doctor of Medical Science degree.

Albert Schaper
... is a Senior Manager in the Berlin office of Arthur D. Little. His main areas of interest are related to strategy development in the pharmaceutical industry with a focus on corporate, market and product strategies. Schaper is an MD, holds an MBA from HSEBA and worked for Wellcome before joining the firm.

Frédéric Thomas
... is a Senior Manager in the Paris office of Arthur D. Little. He has been with Arthur D. Little for over five years primarily working in the pharmaceutical industry. He graduated in business administration and holds an MBA from HEC. Currently he works for major companies in pharma and generic industry, primarily in the area of Strategic Marketing and Business Modelling, including pricing.