Patent issues and future trends in drug development

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Abstract

The global biopharmaceutical industry has been one of the most productive and profitable industrial sectors; however, the drug development process remains risky and expensive, with no guarantees of success. The industry believes that a system for the effective intellectual property protection is key to its ability to maintain innovation for drug development. But some critics think that the market exclusivity offered by patents simply allows companies to maximise profits without benefiting patients.

Social issues such as patient access to new AIDS treatments and political issues such as international trade agreements mean that the manner in which pharmaceutical companies operate at a business level is becoming subject to closer scrutiny.

INTRODUCTION

Over the last 30 years, the biopharmaceutical industry has been successful at launching nearly 1,400 new chemical entities as human therapeutics, and achieving considerable medical advances as a result.[1] The pharmaceutical industry has also proved to be an extremely profitable industrial sector, and growth rates in the double-digit range have been commonplace for the many of the major companies. However, drug development process is a risky and expensive process and several technological hurdles remain. Furthermore, the environment in which the industry operates is becoming ever more competitive. Social issues such as patient access to new medicines and political issues such as cost containment and international trade agreements mean that the manner in which pharmaceutical companies operate at a business level are subject to closer scrutiny.

With stock market analysts suggesting that companies will have to triple their annual launch of new chemical entities to stay competitive and innovative, the pharmaceutical industry faces considerable challenges in order to remain successful.

R&D INVESTMENT

The biopharmaceutical industry invests considerable amounts of its revenue back into R&D. As an industry it is generally regarded as being more R&D-intensive than others (such as the electronics, communications and aerospace) in the technology sector.[1] For major pharmaceutical companies it is common to have R&D-to-sales ratios around 15 per cent (Figure 1). For biotechnology companies, this ratio can be considerably higher. The level of investment is illustrated by the fact that between 1990 and 2000, biotechnology R&D expenditure increased by 262 per cent, whereas that for pharmaceuticals rose by 121 per cent over the corresponding period.[1] At present, with the most profitable products, US companies are in a better position to spend more on R&D than their European and Japanese counterparts (Figure 2).

The tendency to maintain a high level of spending on R&D seems set to continue. This is because it is believed that greater expenditure on R&D will translate into easier access to the new technologies of genomics and high-throughput screening (HTS). Biopharmaceutical companies are hoping that these technologies will result in

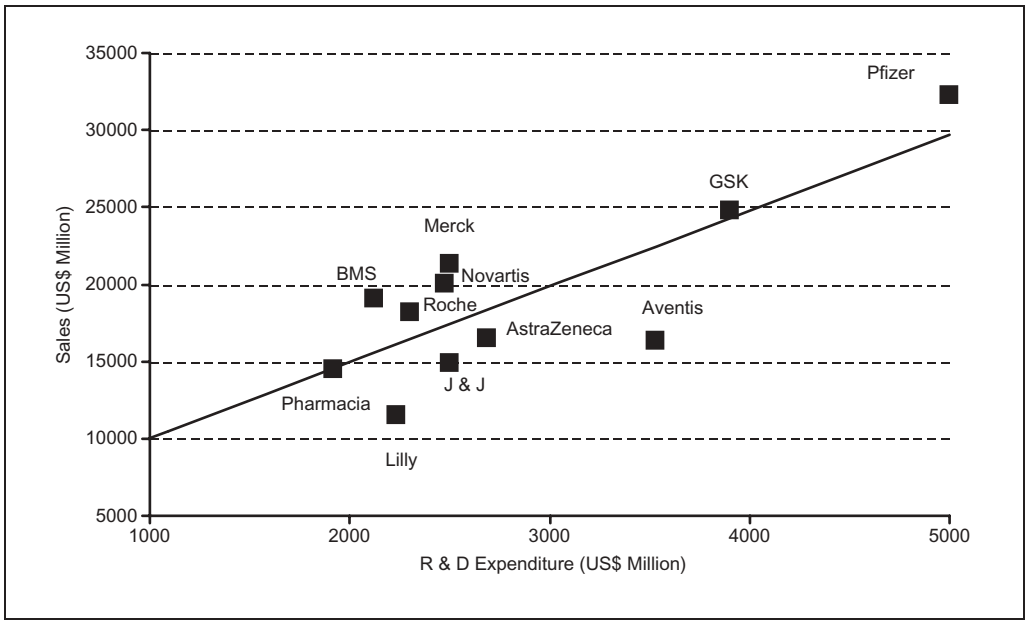

Figure 1: Pharma R&D and sales of major companies (2001)
Source: Company reports and press releases

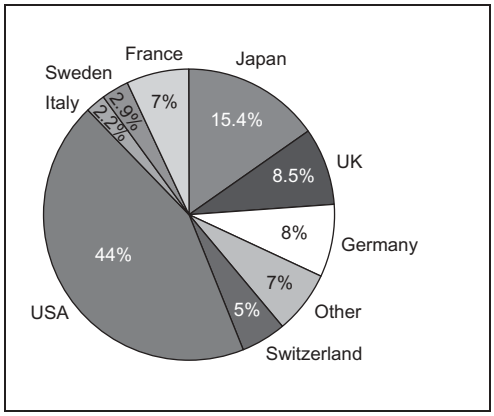

Figure 2: Global split of pharmaceutical R&D
Source: EFPIA, PhRMA, ABPI, CMR International

potential leads for future blockbuster drugs.

Any failure to increase R&D could be taken as a failure to invest in the future

In fact, companies that reduce R&D spending to improve their bottom lines may cause worry among the investment community. Any failure to increase R&D could be taken as a failure to invest in the future. Yet, at times, companies have had good reason to evaluate whether year-on-year increases in R&D spending are justifiable. For example, during the period between 1996 and 2000, there was some concern among the major companies, as the rate of pharmaceutical R&D expenditure began to outpace that of sales; however, more recently, the R&D expenditure rate has been brought into line with that for sales.

THE INNOVATION CHALLENGE

Despite the heavy investment in R&D and media coverage of new technologies such as genomics, there is a worry that the biopharmaceutical industry is becoming less innovative.[2] Although many companies have increased their R&D expenditure considerably over the last few years, this has not resulted in a notable increase in output of new chemical entities.[1–3] In fact, the rise in R&D expenditure has been accompanied by a steady decline in new drugs reaching the market.[1,3] In 2001, the output of the global biopharmaceutical industry in terms of new drugs was the lowest in 10 years. Only 31 new drugs were recorded as having been launched by the industry as a whole during 2001 and many of those that did reach the market came from small biotechnology companies with limited funding.[3] Industry observers did not

Only 31 new drugs were launched during 2001

anticipate any dramatic improvement in new drug output for the major companies during 2002.[3]

An immense cost is involved in successfully getting a drug to market, now estimated at around US$800m.[4] In addition, the considerable failure rate makes the process highly risk-intensive. Despite the increased use of new technologies, it is estimated that only about 15 per cent of new drugs entering development subsequently reach the market.[5] This places a substantial burden on companies trying to get a return on their R&D investment. The chances of a new drug in development reaching the market increases with each stage of the R&D process, but the route is still far from straightforward. Even at the latter stages of development, the failure rate is considered by many in the industry to be too high.[5] Success rates from Phase III to market can range between 50 per cent and 70 per cent.[5]

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CROs are now involved in 60 per cent of clinical work

CREATING THE RIGHT ENVIRONMENT FOR DRUG DEVELOPMENT

The pharmaceutical industry has made a concerted effort to restructure and reorganise its functions and processes in order to maximise the efficiency of its R&D operations, thereby achieving fast development times and a prolonged competitive advantage in the marketplace.[1] Companies that are successful in this respect are ones that not only have the right systems in place to take advantage of scientific breakthroughs, but also have the right environment for innovative processes downstream to flourish.[1] This can be difficult given the fact that R&D is a scientific endeavour and has to be balanced with commercial considerations.

A company culture that thrives on innovation will be increasingly important

Creating a company 'culture' that thrives on innovation and employment will be increasingly important. As many of the major pharmaceutical and biotechnology companies become larger through mergers, this will become harder to achieve. This is because company culture is a mixture of tangible and intangible factors that regulate the behaviour, practices and attitudes of everyone involved in getting a drug to market. It also involves knowing when to rely on in-house capabilities and when to take advantage of skills that exist externally.

Making use of external partners, such as contract research organisations (CROs), can go a long way to expediting drug development. Pharmaceutical and biotechnology companies can concentrate on their core competencies while the CRO specialises on providing the clinical trial services. Outsourcing trials is an increasingly popular option for pharmaceutical and biotechnology companies (Figure 3), as highlighted by the fact that CROs are now involved in around 60 per cent of clinical work.[6] With their experience in running large-scale international trials, CROs can provide companies with valuable advice and feedback, so that they can get the best out of the clinical development process. However, the skills of a CRO should complement those within the pharmaceutical and biotechnology company in order to ensure continuing innovation for drug development.

THE IMPORTANCE OF INTELLECTUAL PROPERTY

The development time to first market for each new drug is an important time period for biopharmaceutical companies, since its duration determines the period of marketing exclusivity (patent cover) available to the company to attempt to recoup R&D expenditure. The time taken to develop new pharmaceuticals has quadrupled since the 1960s.[1]

The biopharmaceutical industry believes that its ability to overcome the technological challenges of R&D and to innovate will be affected by the policies of governments. Therefore, among the various conditions it considers important to maintain a healthy research environment is the establishment of a system for effective intellectual property

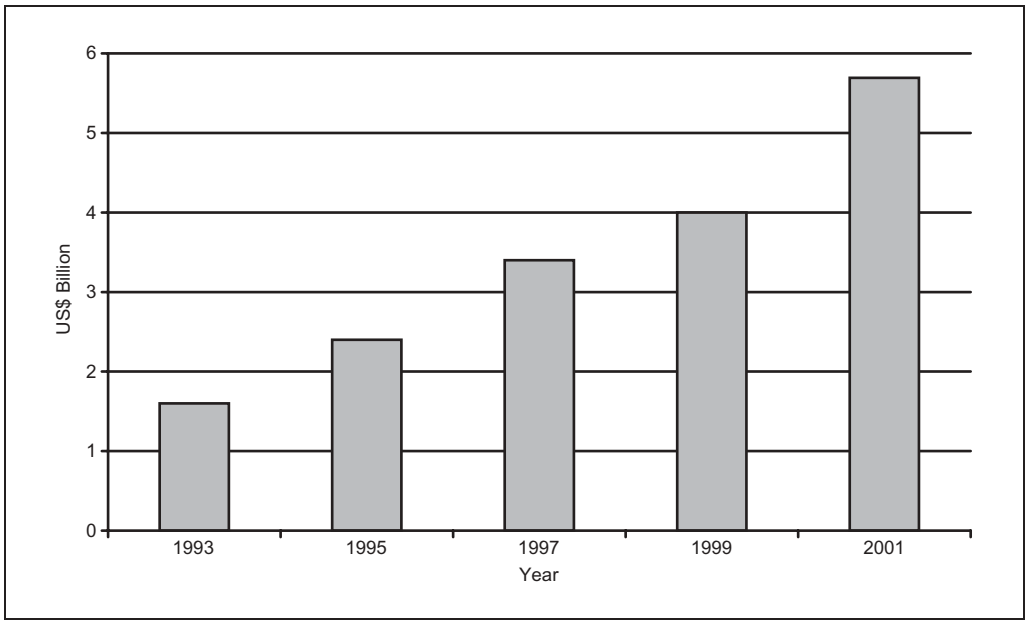

Figure 3: Worldwide spending on CRO services
Source: Centerwatch 2002

protection. A 1988 study of 12 industries carried out by the University of Pennsylvania estimated that around 60 per cent of pharmaceutical products would not have been introduced without adequate patent protection.[7] Furthermore, the existing environment for intellectual property protection can influence the investment behaviour of companies. For example, a study by the US Government found that by strengthening its pharmaceutical patent laws, Mexico attracted investment in both R&D and production facilities of US$103m from US companies between 1991 and 1993.[8]

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Strong patent laws are important to pharmaceutical companies because not only does it allow them the chance to recoup their investments in R&D, it also allows them to reward shareholders who have shown their faith in the company by investing in them.[9] Despite their occasional negative public image, the importance of shareholders to biopharmaceutical companies should not be underestimated. As R&D costs are so high, without their financial backing, few companies would be able to operate successfully. For example, according to Recombinant Capital and Signals' May 2002 Stock Report, only 16 per cent of biotechnology companies have sufficient finances to carry survive for more than five years – and 69 per cent may not be able to carry on for further than a year.[10]

The importance of shareholders should not be underestimated

However, even if a company manages to get its products to market, success is not guaranteed, as there is the threat of competitors to contend with. Companies are increasingly finding it more difficult to dominate the market before competition arrives. Over time there has been a shortened period between first and second products in new market segments.[11] For example, when the beta-blocker drug Inderal was launched it had ten years market exclusivity, whereas 27 years later the protease inhibitor drug, Invirase, for use in the treatment of AIDS, had just three months exclusivity over its rivals.[11]

Fifty of the top 100 pharmaceutical products will come off patent by 2005

Since 2000, a number of high-profile products have been due to come off patent and this has caused considerable worry for pharmaceutical companies. Some observers have predicted that more than 50 of the top 100 pharmaceutical products will come off patent by 2005.[1] Not surprisingly, many companies have strengthened their approaches to defend

their intellectual property rights and this has generated some criticism from sections of the media and from consumer groups.

THE APPROACH TO INTELLECTUAL PROPERTY

Although much of the media attention that is paid to intellectual property occurs when a patent is due to expire, intellectual property protection is central to a company's overall business strategy. Companies have to start thinking about protecting their intellectual property at the earliest stages of research.[12]

Companies must think about intellectual property protection early in their research

Many drugs are now the result of joint projects between companies. Intellectual property becomes an important issue as both parties will have contributed towards the project and will expect to retain certain rights to use the results for their own purposes in the future. When considering intellectual property in these agreements, companies must distinguish between 'background intellectual property' (owned by, or able to be accessed by each party independently of the other) and 'arising intellectual property' (resulting from the actual joint project).[12]

Simply taking out a patent does not confer value on research

An interesting development in this area has been the efforts made by universities, academic spinouts and start-ups to protect their discoveries in order to commercialise their research. However, the world of intellectual property is highly complex and simply taking out a patent does not automatically mean that the research and technologies of these small organisations will be highly valued externally.

One of the problems in valuations is that each stage of the pharmaceutical R&D process must considered in the context of how it contributes to the overall development of the pharmaceutical product. In general, the value is linked to the contribution that the particular part of the process makes to the overall development of the product. For example, if the product is still in the preclinical stages, it has a long way to go before becoming a successful product and therefore the value perceived by researchers may differ significantly from the value placed on it by external observers.

Activities that 'remove risk' from the R&D process are the ones that confer greatest value on a new chemical entity or technology. Although drug discovery is where the patent process begins, the progression to clinical trials is where greatest value is found. Completion of each stage of the clinical trial process (from Phase I to Phase III) brings greater value to the company's compounds or technologies.

PATENTS AND POLITICS

In recent times the issues of pharmaceutical patents and intellectual property rights have extended beyond being a legal and economic concern to encompass political and social views. One of the most contentious issues facing governments and the pharmaceutical industry is patient access to new medicines across the world.

Critics of the pharmaceutical industry have suggested that patents help companies to put 'profits before lives' and restrict patient access to new drugs.[13] They have disputed the idea that patents are necessary for companies to operate successfully and state that governments already offer considerable incentives to companies as a stimulus for R&D investment. For example, many from the Congressional Research Service show that in 1995, the US industry's tax bill after credits was less than 50 per cent of its tax bill before credits.[14] In the current uncertain economic climate these incentives continue to be put forward. For example, in 2002 the British Chancellor introduced a new budget with a tax relief scheme for pharmaceutical companies, according to which R&D tax credits would be issued as a stimulus to those firms investing in technology.[15]

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On a global basis, the laws relating to pharmaceutical patents are in principle regulated by the World Trade

There has been a fierce debate over the price of AIDS drugs

Organization's (WTO) Agreement on Trade-Related aspects of Intellectual Property rights (TRIPS). The TRIPS agreement came into effect on 1st January, 1995, and is considered as the most comprehensive international agreement on intellectual property.[16] In the last few years, there has been a fierce debate over the high price of pharmaceuticals and the efforts to tackle the AIDS crisis in developing countries.

There has been substantial media coverage of patient access to AIDS treatments and the international rules surrounding patents, particularly interpretation of the concept of 'compulsory licensing of patents on essential medical technologies'.[16] Compulsory licensing occurs under strict circumstances when a government allows someone else to produce a patented product, ie a company other than the pharmaceutical company that produced the original brand name drug.

TRIPS Article 31 allows countries to use compulsory licensing for health emergencies

In 1997, South Africa decided to set aside international guidelines on intellectual property, stating that the enormity of the AIDS crisis gave it 'medical emergency status'. Under TRIPS Article 31, countries may use compulsory licensing for domestic pharmaceutical supplies during health emergencies. The problem is that, up until this point, what constituted a 'medical emergency' had never been fully defined.

The elderly have the greatest need for healthcare

In an attempt to block its efforts to use compulsory licensing, the pharmaceutical industry reacted by taking the South African government to court. They claimed that bypassing patent rules would hamper their efforts to research future cures. However, these actions resulted in considerable adverse publicity for the companies involved in the litigation. In a joint statement issued by the parties in which the South African Government confirmed that the South African legislation would be implemented in a TRIPS-compliant fashion, the action by the pharmaceutical companies was withdrawn.

In October 2001 a deal was struck at the WTO ministerial meeting in Qatar allowing countries facing a medical emergency to set aside the usually rigid WTO rules concerning patents.[17] At this meeting it was actually stated, for the first time, that AIDS could be considered a medical emergency for the purposes of TRIPS.

Nevertheless, compulsory licensing remains a difficult and contentious issue, as some campaign groups wish to extend it to cover other diseases that developing countries are tackling, such as malaria.[13] The current approach to intellectual property rights and access to medicines is to promote a more open discussion between all the parties concerned on how countries can make use of the flexibilities of the current WTO guidelines.[16,17] Furthermore, pharmaceutical companies believe that the provision of essential drugs must go hand in hand with health education and disease prevention strategies, which require government involvement.

FUTURE TRENDS

There is no doubt that political pressure will be an additional factor that the pharmaceutical industry will have to contend with in the future. However, because of the continued need for medicines, opportunities abound for companies with the right scientific and commercial strategies.

The next 15 years will see significant demographic changes in all developed nations, most significantly a dramatic rise in the population of those over 65. As the elderly have the greatest need for healthcare, especially for chronic diseases such as Alzheimer's disease and osteoporosis, there will be considerable areas of unmet need that the biopharmaceutical industry can target. For example, in Europe and the USA, the elderly female population is expected to increase by more than 20 per cent by 2006 and it has been estimated that the market for osteoporosis drugs will be worth US$5.7bn.[18] This suggests that

biopharmaceutical companies employing clear and distinctive strategies to take advantage of the drivers for demands for healthcare may well be able to meet their output targets and remain profitable.

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