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R E S E A E C H A R T I C L E

Risks and Opportunities in Development of New Drug

Talagana Praveena[1*], Dr. K. Harinadha Baba[2], S Sivaprasadh[3]

[1,3]*Sri sivani College of Pharmacy, JNTUK, Kakinada*
[2]*Principal Sri sivani College of Pharmacy, JNTUK, Kakinada*

A B S T R A C T

Pharmaceutical development is a costly, time exhausting and uncertain process that takes years to accomplish. In many instances, patent protection expires before a new drug is approved for marketing. Most pharmaceutical firms in the United States and European Union (EU) depend on the exclusivity rights allotted under the U.S. Federal Food, Drug and Cosmetic Act (FDCA), and the corresponding EU authorities to recover their considerable investment in the drug research and marketing approval process. Hence, pharmaceutical companies must understand and use the different forms of non patent exclusivity in both the U.S. and EU in order to win in the global marketplace. Pharmaceutical firms generally obtain patents on their products long before their product candidates are ready to enter market. Since it can take up to 12 years for a firm to obtain market approval, if any, patent protection left on the product at the time of commercializing. To provide pharmaceutical companies with a chance to recuperate their investment in drug research and development and to induce continuing innovation, the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) have enforced numerous provisions to increase the period during which companies can market their drugs free of generic market competition.

Keywords: FDA, EMEA

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Corresponding Author
Talagana Praveena
Sri Sivani College of Pharmacy,
JNTUK, Kakinada
MS-ID: IJCPS3925

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C O N T E N T S

1. Introduction

Regulatory Affairs (RA), also called Government Affairs, is a profession within regulated industries, such as pharmaceuticals, medical devices, energy, and banking. Regulatory Affairs also has a very specific meaning within the healthcare industries (pharmaceuticals, medical devices, Biologics and functional foods). Most companies, whether

they are major multinational pharmaceutical corporations or small, innovative biotechnology companies, have specialist departments of Regulatory Affairs professionals. The success of regulatory strategy is less dependent on the regulations than on how they are interpreted, applied, and communicated within companies and to outside constituents.[1]. This department is responsible for knowing the regulatory requirements for getting new Products approved. They know what commitments the company has made to the regulatory agencies where the product has been approved. They also submit annual reports and supplements to the agencies. Regulatory Affairs typically communicates with one of the Centers (e.g., Center for Drug Evaluation and Research) at the FDA headquarters, rather than the FDA local district offices. Gimps do not directly apply to Regulatory Affairs; however, they must understand and evaluate changes to drug manufacturing and testing activities to determine if and when the FDA must be notified.

Importance of regulatory affairs:

In today's competitive environment the reduction of the time taken to reach the market is critical to a product's and hence the company's success. The proper conduct of its Regulatory Affairs activities is therefore of considerable economic importance for the company. Inadequate reporting of data may prevent a timely positive evaluation of marketing application. A new drug may have cost many millions of pounds, Euros or dollars to develop and even a three-month delay in bringing it to the market has considerable financial considerations. Even worse1 failures to fully report all the available data or the release of product bearing incorrect labeling, may easily result in the need for a product recall. Either occurrence may lead to the loss of several millions of units of sales, not to mention the resulting reduction in confidence of the investors, health professionals and patients. A good Regulatory Affairs professional will have a 'right first time' approach and will play a very important part in coordinating scientific endeavor with regulatory demands throughout the life of the product, helping to maximize the cost-effective use of the company's resources. The Regulatory Affairs department is very often the first point of contact between the government authorities and the company. The attitudes and actions of the Regulatory Affairs professionals will condition the perceptions of the government officials to the company for better, or worse Officials respond much better to a company whose representatives are scientifically accurate and knowledgeable than to one in which these qualities are absent. The importance of the Regulatory Affairs function is such that senior Regulatory Affairs professionals are increasingly being appointed to boardroom positions, where they can advise upon and further influence the strategic decisions of their companies.

2. Risks and Opportunities

The pharmaceutical industry has a number of unusual characteristics that make it very different from what people normally think of as industry. It is also an industry replete with contradictions; for example, despite the undisputed fact that for over a century the industry has made a major contribution to human wellbeing and the reduction of ill health and suffering, it is still regularly identified by the public in opinion surveys as one of the least trusted industries, often being compared unfavorably to the nuclear industry. It is undoubtedly one of the riskiest businesses in which to invest money, yet it is perceived by the general public to be excessively profitable. The major pharm companies rightly promote themselves as being research-based organizations, yet most people believe that they spend more on marketing than on research.[1,2] Despite the acknowledged risks and costs associated with pharmaceutical development, many citizens still believe that pharmaceuticals should be being developed to meet all human needs and that when developed they should be given away to everyone on the basis of need.[13]

This opening chapter aims to provide a basic understanding of how the industry works and attempts to provide an explanation for some of its contradictions. The objective is to provide a backdrop to the business so that the challenges of the issue of pharmaceuticals in the environment can be better understood. Note that the words "medicine," "pharmaceutical" and "drug" are often used interchangeably and the word "drug" can also mean both a medicine and an illegal substance, depending on the context. In this chapter the word "pharmaceutical" is arbitrarily assigned to the end-products of the pharmaceutical industry that are used by patients. The word "drug" is mainly used for potential pharmaceuticals whilst under development by the industry.

Human beings have been using "drugs" to treat illness and disease for more than 3000 years. A few dozen drugs of plant and animal origin were already recorded in China around 1100 BCE and by the end of the 16th century the Chinese were using at least 1900 different remedies.3 Today Traditional Chinese Medicine recognizes more than 13 000 drugs. Outside China, the first known pharmacopeia, the five volumes of De Material Medica, were written in the first century CE by Discords, a Greek botanist. Herbal practitioners of this early period have been identified in many indigenous populations across the globe, such as North and South America, India and Australia. In the later mediaeval period, herbalism flourished in both the Islamic and Christian parts of the world. This tradition continued up to the 17th century, encompassing the work of Paracelsus in Switzerland and Culpepper in England. Culpepper's work, The English Physician, published in 1652, was one of the first English language pharmacopeias.

As the pharmaceutical industry seeks to transform drug development, there is a growing consensus that traditional cost-cutting and productivity-enhancement methods have largely run their course. There are, however, an array of new business tools and platforms that can help companies leverage their assets more effectively in managing the three principal sources of risk that currently interact to push drug development costs higher. These are:

Portfolio risk:

The uncertainty related to accurately assessing a candidate drug's clinical utility and value

Operational risk:

The logistical and management challenges involved in delivering robust clinical information about a candidate drug to the right sources, in a timely manner

Resource risk:

Exposures arising from imbalances between the fixed-cost base that supports operations and the requirement to deliver clinical results that are useful and relevant to regulatory decision-makers.

The Cost of New Drug Discovery and Development:

The development of a new drug requires a major investment of capital, human resources, and technological expertise. It also requires strict adherence to regulations on testing and manufacturing standards before a new drug can be used in the general population. All these requirements contribute to the cost increases for a new chemical entities (NCE, i.e., new drug candidate) research and development (R&D). The central question raised by this trend is who will pay for new pharmaceutical R&D?

The risk component:

Risk in the pharmaceutical industry is the result of scientific, regulatory and economic uncertainty. The first two risks create the lengthy development time and thereby the economic risk. The longer the scientific development time, the greater the likelihood that a competitor will make the discovery first and thereby greatly diminishes the possibility for a return on the R&D investment of the innovator. Regulatory uncertainty occurs because the time required for new drug approval further delays product marketing, and because marketing approval is not assured.

Pharmaceutical firms are attempting to reduce risk by making the decision to discontinue work on less promising drugs earlier. A drug may be viewed as less promising for scientific or economic reasons. A part of this rationale is that more payers are demanding evidence of cost effectiveness in their particular covered populations before agreeing to pay for a drug, thus raising the economic success bar for all drugs entering R&D before they ever reach the market. The trend towards earlier abandonment of marginal drugs indicates a strategy for coping with increased risk. Another measure of risk is the rate at which drugs entering R&D are approved for marketing. By one estimate, the overall success rate for all investigational drugs tested in humans anywhere in the world from 1983 to 1994 was 21.5%. In this study, the highest success rate was for anti-infectives (28.1%), whereas the lowest rate was for central nervous system drugs (14.5%). Again, the message is that the probability of success is fairly small, it is not equally distributed across therapeutic categories, and innovative drug development is a risky endeavor. Further evidence of risk is found in the highly skewed nature of sales for approved NCEs. For NCEs introduced between 1988 and 1992, the top decile (10%) of drugs (by sales dollars) accounted for 56% of overall sales of the cohort of NCEs studied. In practical terms, it means that unless a company can routinely and frequently develop a "blockbuster" drug, the funds to support additional research will diminish. In summary, the combination of long lead-times from discovery to NDA approval, the high probability of failure for compounds entering clinical testing, and the unpredictability of sales once a product is marketed creates a risky business environment. Decisions to fund clinical trials are critical to economic success, and the stakes increase substantially as drugs move through each successive clinical phase.

Protection of intellectual property:

Nearly all countries have some form of protection for intellectual property. Often this is a patent law that confers a monopoly on the innovator for a specified period of time. For pharmaceuticals, the most common time period is 20 years from the time the sponsor files for the patent. Intellectual property protection (in this case by patents) is important, because the cost of innovation is high, whereas the cost of imitation is low. The development costs for a new drug are essentially an investment in knowledge, whereas duplication of the new compound is a simple technical matter. This is an especially important issue in pharmaceutical research because of the long lag time from discovery of a novel compound to marketing. Although recent changes in patent law have increased the period of protection, the effective patent life was estimated to be 11.4 years for NDAs approved in 1995.

Therapeutic competition:

The market for innovative new pharmaceuticals has become so competitive that patent life no longer confers a significant monopoly, because more than one company may be developing compounds with similar mechanisms of action, even though the chemical compounds are different and can each therefore be patented. Two recent examples illustrate this trend. Fluoxetine (Prozac, Eli Lilly), an antidepressant, was the first drug in the selective serotonin reuptake inhibitor (SSRI) therapeutic class and was approved in December 1987. The next SSRI product was sertraline (Zoloft, Pfizer), which did not receive marketing approval until four years later, but still well within the patent protection period for Prozac. On the other hand, Celecoxib(Celebrex, Pfizer) and rofecoxib (Vioxx, Merck) were the first two COX2 inhibitors to be approved (in December 1998 and May 1999, respectively), only five months apart.

Generic competition:

Competition from generic products is rising throughout the world. It was given a major enhancement in the US market with the 1984 passage of the Hatch-Waxman Act (also known as the Drug Price Competition and Patent Term Restoration Act). The Act had the dual purpose of restoring some of the patent erosion that occurs during clinical trials and regulatory review, while increasing price competition for pharmaceuticals by significantly reducing barriers to the entry of generic drugs following patent expiration.

Public policy issues:

As well as the regulatory and market forces described above, there have also been significant public policy changes (in addition to the Hatch-Waxman Act) that have shaped the pharmaceutical R&D environment. The impact of these changes may be difficult to quantify, but the direction of their effects can be easily discerned.

Value of new drugs:

At a time when pharmaceutical expenditure is rising and the cost of pharmaceutical R&D is being criticized, it is

appropriate to ask whether innovative drugs provide value for money. This is a germane question, as attempts to reduce pharmaceutical expenditure generally focus on constraining the use of newer drugs. Does such a strategy have adverse consequences for today's pharmaco therapy and tomorrow's innovations. As just one example, Fuchs examined inflation-adjusted Medicare expenditure and found that it increased at 4-5% per recipient per year at the same time that GDP was increasing at 1.2% annually (Fuchs, 1999). He attributed the increase to the use of new medical technologies (including drugs) and suggested that there was a positive effect on life expectancy and the health status of the elderly. Other investigators have made similar observations and noted that improvements in life expectancy rarely translate into a lower cost of care over a person's lifetime. For example, use of antibiotics to prevent deaths from infections can cause people to live longer and hence to die from heart disease and cancer, which typically entail even greater costs. This is the dilemma and the lesson; the value of pharmaceutical innovations often cannot be captured in conventional accounting calculations.

Value and cost summary:

Pharmaceuticals create value in terms of reduced non-drug healthcare expenditure as well as contributing to improvements in patient quality-of-life that often defy quantification. But what about the cost of these benefits in terms of R&D investment and payments for using the products? In addressing this issue, we assume that few would want to turn back the medical care clock to the time when mercurial diuretics and sulfonamides were standards of care. The more pertinent question then is, how to adequately finance pharmaceutical R&D.

The task of discovering and developing novel NCEs is unusual, if not unique, among business enterprises because it is financed almost entirely by the private sector although many regard the results, such as improved health, as a public benefit. The private sector status of pharmaceutical research means that the industry must generate sufficient income (and make a sufficient return on investment) to cover the cost of developing the next generation of NCEs. Since health care is viewed differently than consumer products, the drug development activities of the pharmaceutical industry are examined closely and subjected to a higher standard of performance than other private sector businesses. There is an expectation that pharmaceuticals will be generally affordable, and that industry resources will be used to develop needed therapies.

3. Regulatory Compliance

Numerous studies have found that the drug development processis highly expensive and that these costs have trended significantly upward for decades. Many factors a ect the cost of drug development, but two of the key basic elements are time and risk. Development times increased substantially from the 1960sthrough the 1980s but overall remained relatively stable during the 1990s. Development times did not directly contribute much to the rapid increase in pharmaceutical R&D costs in the past two decades. However, if clinical trials become largerand more complex, and the costs of inputs to the development process increase faster than inflation, the "time costs" associatedwith the investment of resources in new drug development will increase in absolute terms, even if development times remain the same. Indeed, there is evidence that the clinical trial process has become more extensive and complex in the past few decades. situation is similar for drug development risks. By development risk, we mean the likelihood that development of a drug will be terminated owing to e cacy, safety, or commercial concerns. High drug failure rates contribute substantially to R&D costs, whether or not these costs are otherwise increasing. the rate at which pharmaceutical firms successfully develop investigational compounds for marketing approval by regulatory agencies is an important indicator of the e ectiveness of the drug development process. Processes and technological innovations that can improve the predictability of outcomes for new compounds can therefore significantly increase theproductivity of new drug innovation.

Historical literature focusing specifically on the quantification of drug development risks is fairly robust. Fore mentioned research on drug development costs includes estimates of drug development risks. Early research on development risks suggested that clinical approval rates for self-originated drugs in the 1960s were in the neighborhood of onein eight. Subsequent studies indicated that development risks fell in the 1970s, with approval rates averaging approximately one in five; the risk levels pertaining to the 1970s remained fairly stable to the mid-1990s.

clinical approval success rates and clinical phase transition analyses for the investigational compounds that entered clinical testing between the mid-1990s and the early 2000s from the 50 largest pharmaceutical firms (as determined by sales). We analyze approval success rates and phase transition rate trends within this period for new com-pounds as a whole and by therapeutic class. the data are also stratified by product type (large molecule vs. small molecule)

Success-rate trends:

Trend in the overall clinical approval success rates for new drugs over this period; estimates showed that approximately one insix new drugs that entered clinical testing during each of thesesubperiods was eventually approved for marketing. However, there were small di erences between the two subperiods with respect to the estimated clinical phase transition rates. The results suggest that the failures occurred somewhat earlier in the clinical trial process (phases I and II) for drugs initiated into clinical trials during the later subperiod. There are at least two good reasons for the generally higher clinical approval success rates for licensed-in compounds. First, these compounds have generally undergone some screening or testing

Prior to licensing and have been shown to be promising candidates for marketing approval:

Thus, there may be a screening ect for new drugs that are licensed-in. Second, it is likely that many ofthese licensed-in drugs were acquired after some clinical testinghad been done on them. Although drugs may be licensed-in at any point during the development process, including during the

preclinical period, later clinical phases are associated with higherapproval rates. We do not have data on when in the development process each of the licensed-in drugs was acquired, but if, forexample, the average licensed-in drug was acquired at phase II,then we would expect higher clinical approval success rates for the licensed-in group for that reason alone.

Clinical approval success rates by source of the compound:

As expected, the estimated overall clinical approval successrate is substantially higher for the licensed-in drugs than forself-originated drugs (27 vs. 16%). However, the estimatedtransition probabilities for phase III and regulatory revieware identical for licensed-in and self-originated drugs. The higher estimated clinical approval success rate for licensed-in drugs derives from higher transition probabilities at phases I and II. this suggests that many of the licensed-in drugs were acquired after phase I or phase II testing had already been conducted by the licensor.

4. Conclusion

United States FDA and European medicines agency have enforced numerous provisions to promote innovation by introducing exclusivity strategies which will exclude innovator from unnecessary competition from others. Within the exclusivity period no other application related to the drug product is accepted. In this span of time innovator will be the monopoly in market and no other will compete with his product. The expected revenue fall of major drug companies as they face patent expiration of key drugs, the decline in new product introductions, ongoing cost-containment efforts in healthcare expenditures in established markets in the United States and Western Europe, and pharmaceutical industry growth in emerging markets, have laid the foundation for innovator-drug and generic-drug companies to develop strategies to respond to these changing industry fundamentals. The net result is a blurring of the traditional strategic boundaries between innovator-drug and generic-drug companies. Innovator-drug companies are seeking to diversify and build their positions in generics, which includes product positions in emerging markets. In turn, the major generic-drug companies have to decide how to best avail themselves of the large opportunity resulting from the wave of patent expiries as well as their own diversification into new drug development

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