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STRATEGIC RESEARCH: A Practical Handbook for Phase IIIB and Phase IV Clinical Studies

Chapter 3. What Makes It Different?

This article is the third part of a 15-part series from STRATEGIC RESEARCH: A Practical Handbook for Phase IIIB and Phase IV Clinical Studies by Hugo Stephenson, MD, President, Strategic Research & Safety, Quintiles.

In contrast to registration research, which involves a high-risk investment in products that may be many years away from approval, Phase IIIB and IV research represents an investment in products that are either already on the market and in use by the general public, or are at least expected to become available in the near future. Conducted in a different regulatory and commercial environment, strategic research is normally associated with greater design flexibility, increased cost sensitivity, and greater market awareness.

The Increasing Cost of New Drug Approval

Although pharmaceutical research and development spending has increased steadily over the past two decades, the number of new drugs approved has tended to trend downward since 1997. Behind this trend is the increasing average cost of bringing a drug to market.[1]

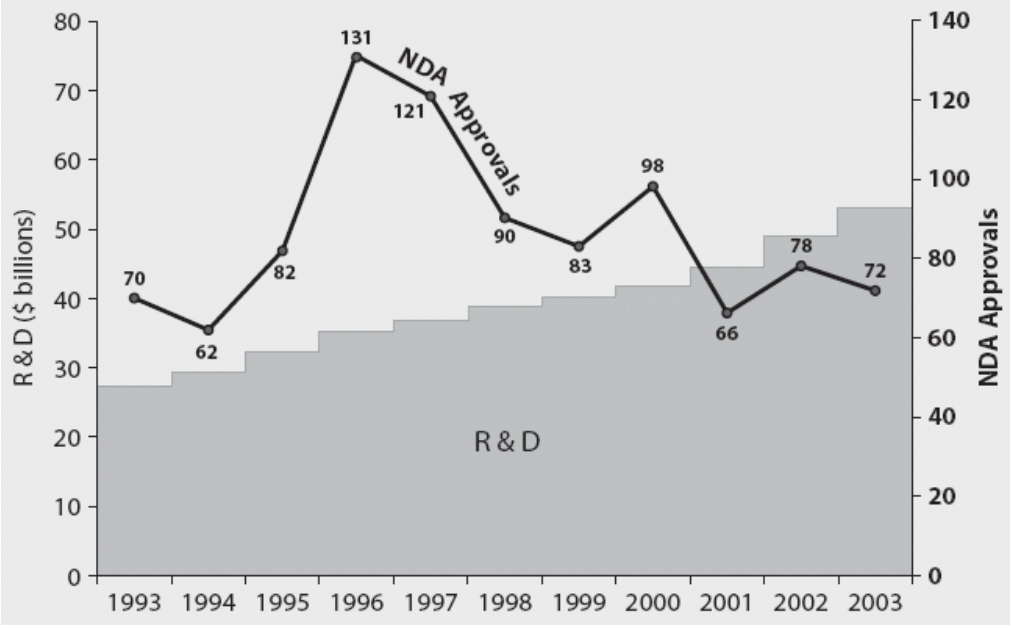

Figure 3. Global Pharmaceutical R&D spending in billions of dollars (shaded) versus the number of NDA approvals granted by the FDA (line).

Design Flexibility

Pharmaceutical companies are reluctant to experiment with non-standard designs for their registration research given the conservative nature of the regulatory environment and its associated costs. Since marketing approval is a necessary milestone for the commercialization of any drug, the new drug application and review process represents a significant hurdle for new products. Companies want to put their absolute best foot forward during this process to minimize potential approval delays and restrictions that could result if they followed non-standard approaches to clinical research.

The pharmaceutical industry has made a science of understanding how regulators think during the approval process. This understanding represents a familiarity with all written regulatory requirements as well as knowledge of how these written requirements have been interpreted in practice. In much the same way as written legislation is given depth through a history of judicial interpretation, the filing strategy for a new product gets more complex as more regulatory advisories and decisions further define the approval process – adding ongoing costs to the drug development process. Armed with experience in the regulatory decision-making process, pharmaceutical companies do not embark on the long and expensive drug development process only to skim the bar at the time of NDA submission. With up to $800 million for Phase I–III research at stake, companies feel that they have little to gain and much to lose by deviating from traditional approaches to study design, monitoring, data collection, and endpoint analysis during registration research. If the company cannot afford to take the most risk-averse approach on the basis of the drug's expected commercial potential, it will shelve the molecule and work on another.

Once companies receive a favorable response to their NDA submission, however, they can be less conservative in the research they support. No longer fearing a loss of their earlier investment on a regulatory technicality, companies can now design studies based on good clinical practice and scientific imagination rather than on regulatory expectations. The relative freedom of strategic research explains why innovative designs, processes, and technologies have been more broadly adopted in Phases IIIB and IV, and why efficiencies emerging from these new approaches have had a very limited impact on the increasing cost of drug development associated with Phases I–III. The various study designs that can be valuable after submission of the NDA are described in detail in chapter four.

Different Operational Alternatives

Just as variation from the randomized controlled trial format is more common in Phases IIIB and IV than in registration research, companies are also more receptive to different operational approaches when conducting strategic research. Because products are now available in the real world, it is possible to do naturalistic studies. It is also possible to study products for indefinite periods of time. In addition, since operational processes can be adapted to reflect an increased confidence in the effectiveness and safety of a drug after pivotal trials are completed, sponsors are turning to creative methods such as remote monitoring and direct-from-patient data collection to conduct their studies more efficiently.

For example, active surveillance studies are frequently performed to evaluate the safety of products in the post-marketing period. To ensure that these programs encourage maximum patient enrollment and avoid selection bias, it has become common for safety surveillance programs to seek a waiver of informed patient consent from ethics committees or IRBs. This waiver is usually granted on the basis that patients are not subject to any additional risks as a result of a naturalistic study protocol, and privacy is protected by the appropriate de-identification of data.

Cost Sensitivity

Registration research is usually funded from the consolidated R&D budget as a cost of conducting business. Phase IIIB and IV research, in contrast, is most often funded from an annual brand budget and internally accounted for as a cost of goods sold. Manufacturers often perceive this research as a voluntary investment in a brand, which therefore competes for funding with other activities such as medical education and communications, advertising, sales teams, and sponsorships.* This is usually the case even when the responsibility for designing and managing clinical research is appropriately separated from a company's marketing function. Because these competing activities are often relatively short and cheap, strategic research is under greater pressure than registration research to prove itself valuable, timely, and reasonably priced while remaining in compliance with good clinical practice.

Once approved, most products will generate considerable return with no additional research investment. As a result, Phase IIIB and IV research is funded on a project-by-project basis with an emphasis on maximizing the value of each study to the company. Companies ask themselves, "How much can I gain if I do this study?" and "How much could I lose if I don't do it?" thus regularly balancing their opportunities and public health responsibilities against cost and risk.

Doing Research on a Brand Budget

A cardiovascular study conducted for registration purposes cost a major pharmaceutical company almost $6 million, although it involved fewer than 500 patients and only 25 sites. The company reproduced the study, using the same number of patients and sites but with a different patient population for just under $1 million. Faced with a limited budget for the brand, and no longer constrained by regulatory requirements, the pharmaceutical sponsor willingly considered alternative approaches to site selection, site monitoring, and data capture, which resulted in significant cost savings.

Invariably, by competing with other non-research activities for funding, and by requiring project-by-project justification for investment, Phase IIIB and IV research programs are much more cost sensitive than is registration research. For this reason, strategic research programs have needed to adopt more creative study designs and cost-effective operational approaches, such as electronic data collection, centralized project coordination, remote monitoring services, direct-from-consumer data collection, and offshore data processing.

Market Awareness

Conducted in parallel with a flurry of commercial activities – advertising, product detailing, medical education, conferences, and speaker tours – effective execution of Phase IIIB and IV research demands an intimate understanding of the commercial side of the pharmaceutical business. Phase IIIB and IV research involves brands, not just drugs, and needs to be intimately coordinated within a much bigger picture of business activity.

In earlier phase studies, the company is researching a molecule; somewhere between discovery and launch that molecule becomes a brand. Clinical researchers who worked with

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* Even though regulators have increasingly demanded additional post-marketing studies as a condition of approval, there have been few repercussions for the many companies that have not yet fully met, or even commenced, their regulatory commitments.

the molecule UK-92480 faced different challenges and market expectations than those working with Viagra, as the molecule is known today.

Unlike registration research, Phase IIIB and IV research is subject to promotional laws and restrictions that apply to all business activities involving marketed products. In addition, a whole new set of pharmaco-vigilance reporting responsibilities also apply. Whereas earlier clinical research was the only business activity involving a product, any ongoing research conducted after regulatory filing becomes just a small part of a much bigger brand support machine—tolerated by commercial operations on the basis that its execution does not significantly interfere with them. Understanding the roles of investigators, key opinion leaders, medical directors, sales representatives, nurse advisors, sales managers, and brand managers—some of whom may have little or no clinical research experience—is critical to the success of working within a much bigger team, and ultimately to the success of any research activities.

Conclusion

Phase IIIB and IV research represents an upside opportunity for products that are either already on the market or are expected to generate revenue in the near future. As a result, pharmaceutical companies are more open to deviating from traditional approaches to clinical research than when product approval remains at risk. In addition, shorter term return on investment expectations, requirement for greater commercial sensitivity, and greater competition with non-research activities for funding creates demand for cost effectiveness, design flexibility, and market awareness not normally associated with registration research.

Reference

1. NDA data appears on www.fda.gov/cder/rdmt/pstable.htm. Pharmaceutical R&D data is from CMR International 2004 R&D Factbook, Center for Medicines Research International (2004). www.cmr.org.* *Note: All citations to websites listed in this book were verified in May of 2005.