

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

### **Chapter 1. What is Strategic Research?**

*This article is the first 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.*

#### **What Is Strategic Research?**

Clinical trials are the scientifically rigorous way to measure whether new drugs are safe and effective in patients. Since the first randomized controlled trial (RCT) conducted in 1948, regulatory agencies have used clinical trials to determine whether a new drug is ready for the public.<sup>1</sup> Over the past decade, however, it has become clear that the clinical trials required by regulatory agencies for approval leave many important questions unanswered. The pharmaceutical industry now regularly conducts clinical research after the submission of a new drug application to provide information to providers, patients, and payors about drugs that are close to receiving marketing approval or that the general public is already using.

These studies are called Phase IIIB and IV studies because they follow the Phase I–III clinical trials required by regulatory agencies for initial registration. Increasingly known as strategic research they have become a critical part of every peri- and post-marketing product strategy. Companies choose to conduct them for many reasons, such as monitoring product safety and discovering new uses for the drug once it is on the market. These studies address a larger audience than the earlier phase studies, including doctors, patients, insurers, and the media, in addition to the regulatory agencies, and take a wider variety of forms because they are not restricted to the randomized controlled format that regulators require for drug approval.

In the past, this research has been negatively associated with "seeding" studies whose main goal was to give physicians an incentive to start prescribing a drug. Companies would design such "studies" to gather trivial data that resulted in scripts for thousands and thousands of new patients. Since the passage of the Medicare and Medicaid Protection Act of 1987, the regulatory environment in the United States has become hostile to these types of seeding studies, and reputable organizations no longer conduct them. Similar trends are emerging in Europe. With the decline of seeding studies and greater emphasis on product safety has come greater recognition of the scientific importance of strategic research.

Scientifically rigorous Phase IIIB and IV studies have had significant impact on the marketplace. In the late 1990s, Warner-Lambert and Pfizer used such studies to show that Lipitor, a new cholesterol-lowering drug, led to improved health outcomes as opposed to other drugs already on the market. Lipitor became a new blockbuster drug, while its competitors, Pravachol and Zocor, suffered declining sales. In contrast, Merck's analysis of data from its APPROVe study resulted in the withdrawal of the blockbuster drug Vioxx. This Phase IIIB trial for a new indication famously confirmed cardiovascular risks of long-term exposure. As these examples show, strategic studies can make or break a product.

## Two Stages of Drug Development: Registration and Strategic Research

Today's regulatory environment has divided the drug development process into two stages: obtaining approval to sell a product, followed by generating the information providers and patients need to use the drug most effectively.

The first stage of the drug development process – which includes preclinical research, and Phase I, Phase II, and Phase III trials – focuses on obtaining product approval. Following testing on animals, the early phase trials begin by investigating human pharmacology to determine toxicity (Phase I), explore effectiveness and identify an appropriate dose regime (Phase II), and confirm effectiveness in large populations (Phase III).<sup>2</sup> Often referred to as registration research, these studies generate data for submission in support of a new drug application and are pivotal to any product approval decision.

Since registration research primarily targets the information needs of regulators, it is generally constrained by guidelines, advisories, and past agency decisions that limit research to tightly designed clinical trials. Pharmaceutical companies invest in this clinical research to meet regulatory requirements for drug approval but find that these studies are often too limited in duration of treatment or diversity of patient population to effectively evaluate safety in the general population. Even after research findings satisfy regulatory agencies, many questions remain unanswered. It is here that Phase IIIB and IV studies play a large role.

With the Food and Drug Administration's Acting Commissioner Lester M. Crawford acknowledging a 50 percent product attrition rate during Phase III alone,<sup>3</sup> most companies are reluctant to expand the focus of their research investment until they are confident that a regulatory agency will approve their product. Companies wait for a thumbs-up from regulatory agencies before investing in a second stage of research.

Once a manufacturer no longer needs to focus solely on product approval, they can turn to addressing unanswered questions that could impact optimal use of a product through Phase IIIB and IV programs. This second stage of research has been collectively referred to as late phase, late stage, or peri- and post-marketing, but since market forces can affect the mechanics of this research and the results of these studies can influence market behavior, the industry has come to call it strategic research.\*

Phase IIIB and IV studies cover a spectrum of designs, and range from highly controlled, randomized studies, identical in type to registration studies, to retrospective studies using preexisting databases that can be completed in less than three months. Patient numbers can range from 200 to 100,000, often targeting diverse patient groups including children, the elderly, and patients with complex comorbidities.

Six to eighteen months before anticipated launch, many companies begin reviewing

### Challenging Market Behavior

Preparing for product launches across Europe throughout the year, AstraZeneca announced data from the 2,431-patient STELLAR study in April 2003.<sup>4</sup> By demonstrating that Crestor had greater dose-for-dose efficacy in reducing cholesterol than any of its major competitors, the results of this randomized controlled trial created an opportunity for AstraZeneca to challenge the normal prescribing pattern of physicians.<sup>5</sup>

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\* As an example of how market forces can affect the mechanics of the study: if a product becomes reimbursed during the course of a study, it suddenly becomes much harder to recruit patients.

their data from registration trials in a market context. In developing a brand strategy, a company must judge whether their early-phase research provides the public with enough information to ensure that their drug is most effectively used. Companies can strategically use Phase IIIB and IV research to fill critical information gaps before and immediately after launch.

All gaps are not necessarily closed before launch, and new gaps will emerge during the drug's lifetime. Pharmaceutical companies must regularly review what additional information patients, physicians, insurers, and the media require, making Phase IIIB and IV research an ongoing concern.

Questions answered by Phase IIIB and IV research include: What can patients and physicians expect from using a product? Does this vary from patient to patient? How does it compare with its competitors? What is the drug's safety profile in large populations and over long periods of use? How cost effective is treatment, and what pricing strategy is likely to result in most effective market uptake? Could the product be used to treat other conditions? Could restriction of the product's label limit potential medicolegal liability?

### Phase IIIB

The moment the manufacturer applies for marketing authorization for a particular product, all ongoing clinical research not conducted in line with an approved product label becomes, in industry parlance, Phase IIIB research.\* Pre-approval Phase IIIB studies occur while the regulatory agency is reviewing the submission and usually focus on generating additional

#### Identifying Favorable Product Characteristics

Although numerous drugs are available for the treatment of schizophrenia, each product has different strengths and weaknesses that psychiatrists must balance when selecting the right treatment for each patient. The more information available, the more effectively patients can be matched with the most appropriate treatment. In December 2004, Eli Lilly & Co. published data from a large three-year naturalistic Phase IV study, SCAP (Schizophrenia Care and Assessment Program), suggesting that patients receiving long-term treatment with Lilly's antipsychotic Zyprexa were at lower risk of exhibiting violent behavior than those receiving Janssen's

data to support the product's anticipated launch. Such activities include observational studies that inform treatment guidelines or randomized controlled studies that compare the efficacy of a product against its market competitors. These activities can also include expanded access programs that offer products before they are approved to severely ill patients.

Post-approval Phase IIIB studies investigate the use of approved drugs outside the terms of their approved product label. They are usually conducted to explore new therapeutic opportunities or support changes to the product label. Geodon, a commonly used anti-psychotic drug, was introduced to the market for the treatment of schizophrenia in February 2001. As a result of Phase IIIB research investigating new indications, Geodon received approval for treatment of bipolar mania in August 2004.

Phase IIIB studies, both pre- and post-approval, use products in ways that have not

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\* While Phase IIIB is not a definition formally used by regulatory authorities, the industry does use the term to describe additional therapeutic exploratory and confirmatory studies conducted after the primary regulatory dossier has been submitted.

been approved and are therefore associated with greater potential patient risk than studies performed on approved drugs for already approved uses, called Phase IV research. As a result, Phase IIIB studies usually involve checks and balances to ensure patient safety, including tighter enrollment criteria for subject participation, more frequent and detailed patient follow-up, more detailed adverse event tracking, and more frequent monitoring activities than are normally required in Phase IV.

## Phase IV

Phase IV research investigates approved products used in line with their approval labels. Examples include randomized, controlled trials that are conducted to address questions about comparative efficacy, tolerability, and cost effectiveness of different treatment approaches. Because physicians are prescribing these approved drugs under uncontrolled conditions, observational studies that capture naturalistic data about treatment outcomes over time can also be performed, informing treatment guidelines and best practices. Many post-marketing safety studies take this form. If a drug has been available for a significant period of time, data may be available retrospectively from patient records and files. Note that Phase IIIB and IV trials often occur in parallel, as companies seek to explore expanded uses of the drug at the same time as solidifying the scientific basis for their product's existing claims.

Companies frequently conduct Phase IV studies to monitor product safety under real-world conditions. These studies can avoid the selection bias associated with registration research by involving large numbers of patients who have complicating factors that would have barred them from participating in the controlled Phase II or III trials. Only when a product is used outside the tightly controlled clinical trial conditions of earlier registration research does its true benefits and hidden dangers become apparent.

Phase IV trials can also play a part in a company's appropriate due diligence to ensure that medicines are used most effectively and safely within the community, minimizing harm to patients and ultimately medico-legal risk.

## Conclusion

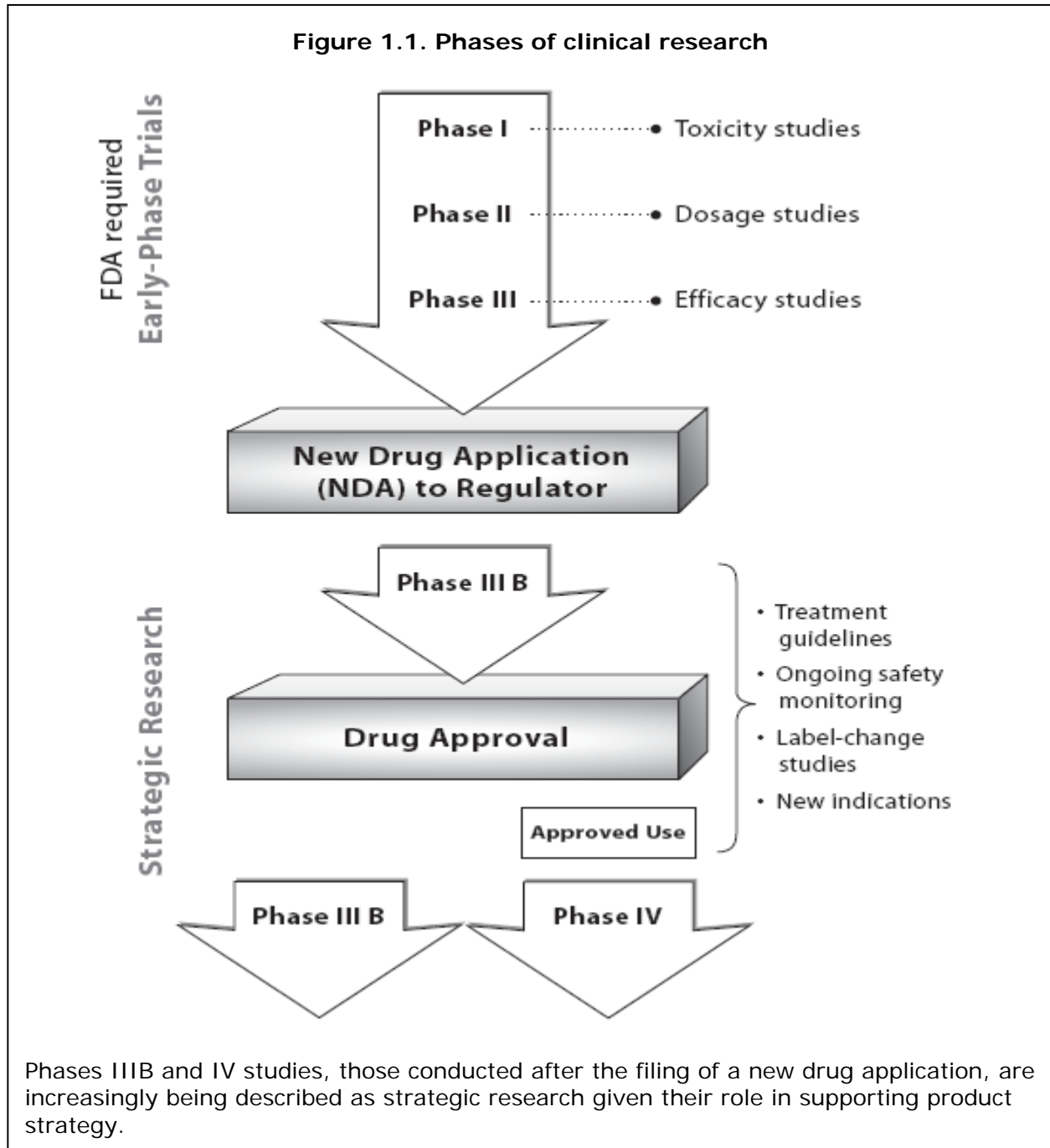
In the past, some late-phase clinical studies gave the field a bad name because they were conducted with the express purpose of getting physicians to prescribe new drugs. As these seeding studies have become illegal in today's more stringent regulatory environment, scientifically valid Phase IIIB and IV studies, always important, have begun to receive more attention. They are used to provide information on safety issues, to assist in the development of more extensive treatment guidelines, to explore new indications, and to compare drugs within the same class with an eye to what patients and payors feel is important about a drug's effects and costs.

### Safety Limitations of Registration Research

A prime example of how registration trials can miss significant safety issues is the case of Rezulin, a diabetes drug that began to be used widely after its introduction in early 1997.

Unfortunately, the number of patients treated in registration studies was insufficient to effectively quantify the product's risk of severe liver damage. These controlled clinical trials only reported rare cases of reversible jaundice by the time that the product was approved in March 1997. But by October 1997, after less than six months of real world use, 35 cases of idiosyncratic hepatocellular injury (resulting in one transplant and one death) had been reported to the FDA. Rezulin was withdrawn from the market in 2000 after an FDA review of safety data showed it to be more toxic to the liver than the newer drugs in the same class, Avandia and Actos.<sup>7</sup>

Strategic research allows manufacturers to address questions about their products that remain unanswered at the time of registration, and that may arise later in a product's lifecycle. As the industry continues to face greater scrutiny, sponsors are discovering that providing more scientific information to a discerning public, to health care organizations and to regulatory agencies is a good investment.



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\* Note: All citations to websites listed in this book were verified in May of 2005.