WHITE PAPER

premier consulting

REGULATORY

Why 505(b)(2) is a Whole Different Animal

OVERVIEW

The three pathways to gain approval to market a drug in the United States share many common characteristics, but each is distinctly different from the others. It's important to know in advance the strengths and weaknesses of each approach when considering a development strategy.

The 505(b)(1), 505(b)(2), and 505(j) approval pathways share the same requirements for FDA approval but differ with respect to the amount of information the sponsor must provide from its own research.

Introduction

In broad terms, the 505(b)(1), 505(b)(2), and 505(j) approval pathways share the same requirements for Food and Drug Administration (FDA) approval. However, the three pathways differ with respect to the amount of information the sponsor must provide from its own research. Generally, 505(b)(1) development is used when the drug under consideration is a new entity and the sponsor – or its agents – will conduct all of the studies required for a New Drug Application (NDA). A 505(b)(2) application, on the other hand, is one for which one or more of the studies relied upon for approval has not been conducted by or for the applicant. In these cases, an applicant may rely on published literature or on the FDA's previous finding of safety and/or effectiveness for the drug. Finally, the 505(j) application is utilized for a generic version of a previously approved product, relying completely on the previously established safety and efficacy data.

The 505(b)(2) pathway can offer important advantages for various types of drug manufacturers in an era of increased competitive pressure. For instance, research-based companies with products facing patent expiration may find that the 505(b)(2) pathway can provide a useful mechanism to extend product exclusivity. At the same time, for generics companies facing the impending "generic cliff," the 505(b)(2) pathway can be a powerful tool to improve the revenue stream. Indeed, products approved through the 505(b)(2) pathway may qualify for three, five, or even seven years of market exclusivity, depending on the extent of the change to the previously approved drug and the type of clinical data included in the NDA.

In the end, the 505(b)(2) pathway can allow companies to move beyond the competitive environment of generics while still enjoying a development process that eliminates most preclinical studies as well as extensive safety and efficacy tests, dramatically reducing costs and time to market.

Because of its advantages, the 505(b)(2) process has had a significant impact on the drug development landscape since its establishment in 1984. But the process is not a simple one. 505(b)(2) success hinges on identifying products that have documented market differentiation, low development risk, and high profit potential. Moreover, the 505(b)(2) pathway comes with unique and demanding requirements that are difficult to navigate. The sections that follow describe many of the advantages and challenges associated with the (b)(2) pathway.

Product identification

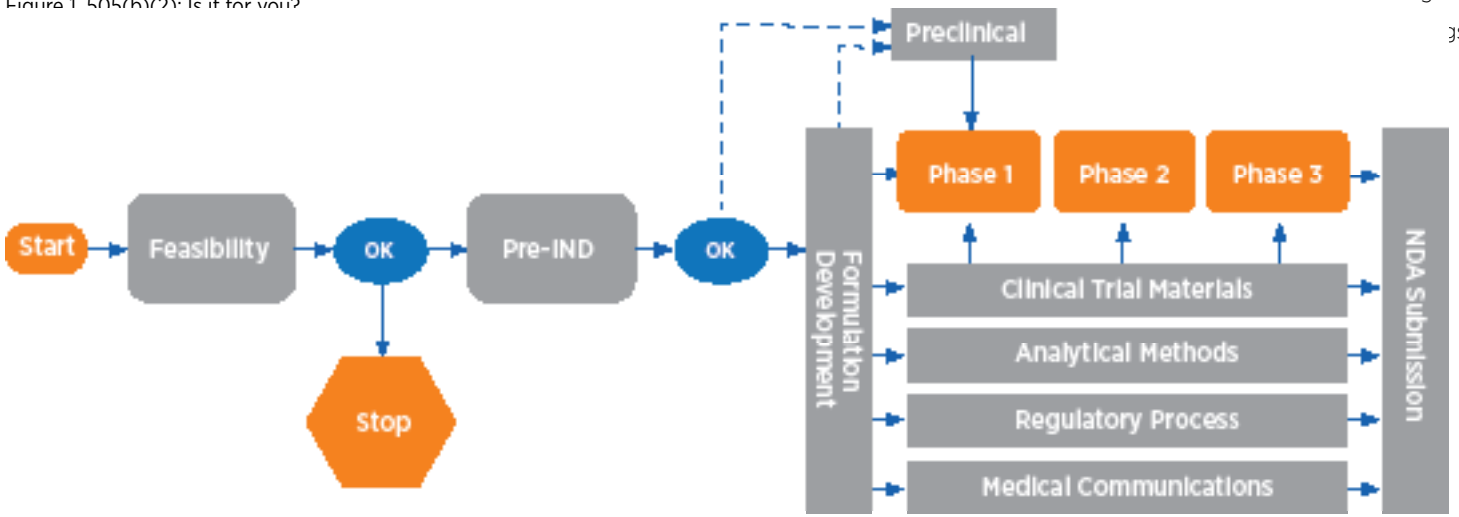
The first step in any drug development pathway is to identify a compound with commercial potential. The viability of any compound should be evaluated based on multiple considerations, including the market segment, product SWOT analysis, production requirements, marketing and competitive examination, investor appeal and, ultimately, profit expectation. This predevelopment process helps defend the value to investors and reduces the risk of costly errors.

In the 505(b)(1) pathway, a novel molecule is selected for development based on its potential effect on human systems. And while a molecule may show promise in shrinking tumors or growing hair, the passage from "promising molecule" to "approved drug" is long, difficult, and expensive. Typically, achieving approval under the 505(b)(1) regulatory pathway can cost the sponsor as much as 15 years and up to a billion dollars.

On the other hand, compounds approved through the 505(b)(2) pathway can often be developed with lower risk, reduced cost, and faster speed to market. While the (b)(2) pathway can be used for any approved or unapproved compound for which there is sufficient public data, it is particularly useful for those compounds that represent a limited change from an approved drug. Ideal candidates include:

- New indications for an approved drug
- Drugs with changes in dosage form, strength, formulation, dosing regimen, or route of administration
- New combination products, including drug/device combinations
- Drugs with new active ingredients
- Prodrugs of an existing drug
- Drug efficacy study implementation (DESI) drugs
- Branded generics

Figure 1. 505(b)(2): Is it for you?



Getting started: Preclinical research, pre-IND meeting, and the IND application

Once product feasibility has been established, a 505(b)(1) drug development program typically requires up to six and a half years of basic discovery work and preclinical – in vitro and in vivo animal – testing. Because the (b)(1) pathway is built on clear guidance and well-established study designs, the (b)(1) preclinical process is straightforward:

- Conduct required studies for animal toxicology, pre-formulation, formulation, and pharmacokinetics
- Complete a pre-initial new drug (IND) consultation with the FDA – required for (b)(1) submission – in which the sponsor presents findings from its preclinical studies in order to gain FDA agreement to move to human testing
- File the IND Application

Compared with 505(b)(1), the (b)(2) process start-up is distinctive in several respects. First, the order of these steps is different. As shown in Figure 1, the (b)(2) process begins with the pre-IND meeting with the FDA, then moves to formulation development, and preclinical studies if necessary, and then to the IND filing.

Second, the goals of the pre-IND meeting are different. In proposing a (b)(2) development strategy in a pre-IND meeting, the objective is to gain FDA input and concurrence with both the preclinical, chemistry, manufacturing, and controls (CMC) and clinical research plans in a way that minimizes the number of new studies required. The "data gap" that is presented during the pre-IND meeting determines the studies that the sponsor must conduct and present as part of the 505(b)(2) NDA.

Third, the number and type of studies required are different. Since the (b)(2) pathway allows the use of public data in lieu of novel trial data, it is possible in some development programs to conduct bridging studies that can preclude the need for either preclinical or clinical studies, or both. Preclinical studies are called for in some (b)(2) development plans, of course, including plans for products that have a new route of administration or when FDA standards have changed since the reference listed drug (RLD) was approved.

Finally, the timing of studies is different. Because 505(b)(2) development plans rely largely on pre- existing data, preclinical and clinical studies can often be started simultaneously and developed in parallel, significantly shortening the overall time to market.

Each of these unique aspects of 505(b)(2) start-up presents its own set of complications. Together, they represent a formidable multicomponent challenge. When mishandled, the early steps of (b)(2) development can end in product development failure. On the other hand, when managed skillfully, these first steps can result in important victories for the sponsor, including reduced costs, a clear path to approval and immediate interest from investors. Sponsors can benefit greatly by seeking early guidance from drug development partners with proven expertise in the (b)(2) approval route.

Phase 1 clinical research

Quality performance, timeline management, and cost control are key watchwords throughout the clinical development process, beginning with Phase 1 studies. Phase 1, first-in-human, trials primarily concern toxicity testing in healthy volunteers. What these studies entail, however, differs depending on the development pathway.

In a standard (b)(1) scenario, the drug is administered to a small number of individuals to determine probable safe dosages and side effects, and to learn how the drug is metabolized and excreted.

In certain instances, the 505(b)(2) pathway enables the Phase 1 process to be reduced to a single study. This study, known as a Phase 1 bridging study, is used to compare the in-human pharmacokinetic properties of the proposed drug product with that of the reference product. Done properly, a bridging study allows a company to reference the established safety information for the original drug.

In 505(j) development, Phase 1 studies compare the test drug and reference drug to establish equivalency. This comparison is often established through a pharmacokinetic bioequivalence study or, in cases where systemic exposure is inadequate, with a pharmacodynamic or clinical endpoint noninferiority trial.

Sponsors can benefit greatly by seeking early guidance from drug development partners with proven expertise in the (b)(2) approval route.

In certain instances, the 505(b)(2) pathway enables the Phase 1 process to be reduced to a single study. This study, known as a Phase 1 bridging study, is used to compare the in-human pharmacokinetic properties of the proposed drug product with that of the reference product.

Phase 2 and 3 clinical research

Phase 2 studies, required in 505(b)(1) NDAs, are designed to confirm the pharmacokinetic profile of the product, ensure safety in patients, and determine the minimum effective dose and the maximum effective, tolerated dose. Upon completion of Phase 2 testing, the (b)(1) sponsor usually meets with the FDA reviewers to conduct an end-of-phase 2 (EOP2) meeting at which the Phase 1 and 2 results are examined and the Phase 3 study plan is determined. For a standard 505(b)(1) NDA, Phase 3 consists of two large, well-controlled studies – often referred to as "pivotal studies" – designed to produce statistically significant evidence of the product's safety and efficacy. These pivotal trials include hundreds or even thousands of patients in a wide age range and with varying levels of disease severity, and allow for multiple concomitant conditions and medications.

In contrast to drugs developed within the 505(b)(1) pathway, certain 505(b)(2) development programs require no Phase 2 or Phase 3 studies. For instance, in some (b)(2) NDAs, substantial safety and efficacy can be demonstrated through a single Phase 1 bridging study, if the systemic exposure is similar to the reference drug. Generally, if any Phase 3 research is required for a (b)(2) NDA, only one study is necessary, versus the two required for (b)(1)-pathway products, and fewer patients may be needed due to the existing safety data available in public literature.

Conclusion

For both the 505(b)(1) and 505(b)(2) pathways, the ultimate goal is to create a differentiated product that is both marketable and profitable. But (b)(2) has become the leading pathway in recent years; in 2012, approximately 50 percent more products were approved through (b)(2) development than through (b)(1). Moreover, within the next few years the share of new drugs approved via (b)(2) is expected to reach more than 80 percent; this growth is a testament to its increasing value in the drug development market.

In the final analysis, 505(b)(2) development is more than just a regulatory pathway, it is a distinctly different animal – a unique strategy that can often result in product approval with lower risk, reduced development cost, and faster speed to market. Sponsors benefit from employing a deliberative, step-by-step approach led by a team of experts with the commercialization, drug development, and regulatory expertise to synthesize a viable 505(b)(2) development plan.

About Premier Consulting

Premier Consulting is a strategic product development and global regulatory consulting company dedicated to helping biotech innovators transform their life-changing ideas and breakthrough science into new medical treatments.

Our end-to-end solutions in strategy, regulatory, nonclinical, clinical, CMC, quality, and commercial help sponsors build and execute development plans that meet regulatory requirements and deliver results for sponsors and the patients they serve.

Premier Consulting
3800 Paramount Parkway
Suite 400
Morrisville, NC 27560

info@premierconsulting.com | premierconsulting.com