



White Paper

Understanding the 505(b)(2) Approval Pathway



Overview

A 505(b)(2) is a new drug application which contains full safety and effectiveness reports, but allows at least some of the information required for approval to come from studies not conducted by or for the applicant. This method gains approval for new drugs in a fraction of the time and cost required by traditional paths.

<input checked="" type="checkbox"/>	Relatively low risk because of existing safety and efficacy information
<input checked="" type="checkbox"/>	Lower cost due to the smaller scope and number of potential studies
<input checked="" type="checkbox"/>	Increased speed due to fewer studies

In the fiscal year 2006, approximately 20% of new small molecule drugs were approved through the 505(b)(2) process; two years later, over half were based on this strategy. Judging from the rate at which we are filing Investigational New Drug (IND) applications today, we expect that the percentage of 505(b)(2) approvals will be greater than 80% within the next few years. The reasons behind the remarkable success of 505(b)(2) are twofold. Because approval can rest in part on data already accepted by the FDA or otherwise available in the public domain, fewer and smaller studies may be required, thus mitigating costs and shortening development time. Unlike generic drugs approved under Section 505(j) where exclusivity can be held for only 180 days, the 505(b)(2) applicant may qualify for three, five or even seven years of market exclusivity, depending on the type of clinical data included in the NDA.

Potential Regulatory Pathways for Drug Products Under Development

Appropriate for drug products that are the same as approved products

505(j) ANDA

Hybrid between an ANDA [505(j)] and a full NDA [505(b)(1)]

505(b)(2) NDA

'Full' Application – Data predominantly obtained from studies conducted by the Sponsor

505(b)(1) NDA

Studies conducted by the Sponsor

The 505(b)(2) Process

Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act was established by the Hatch-Waxman Amendments of 1984 to allow sponsors to obtain approval of NDAs containing investigations of safety and effectiveness that were not conducted by or for the applicant, but for which the FDA has issued an approval. The section was added to avoid unnecessary duplication of studies already performed on the reference drug. However, sponsors must still provide any additional data necessary to ensure that the differences from the reference drug or other existing information do not compromise safety and effectiveness.

Today, 505(b)(2) can provide relatively fast-track approval for a wide range of products, especially for those that represent a limited change from a previously approved drug. Ideal candidates include:

- New indications
- Changes in dosage form, strength, formulation, dosing regimen or route of administration
- New combination products
- New active ingredients
- Pro-drug of an existing drug

505(b)(1) vs. 505(b)(2)

The 505(b)(1) process is what the industry is familiar with; it is executed for new drugs like those discovered by big pharma versus the 505(b)(2) process, which can take an existing drug and makes small modifications, often significantly advancing the medication for the patients' benefit.

Drug Development Timeline			
	Discovery	Preclinical Research	Clinical Studies
505(b)(1)	2-5 years	1-3 years	8-15 years
505(b)(2)	<1-3 years	<1-2 years	2-5 years

An Opportunity in DESI Drugs

The FDA's Drug Efficacy Study Implementation (DESI) program was enacted to evaluate the efficacy of all drug products approved and marketed on safety grounds alone between 1938 and 1962. Although these DESI-approved drugs may continue to be marketed until the administrative proceedings evaluating their effectiveness have concluded, continued marketing is permitted only if a new drug application (NDA) is approved for such drugs.

Currently, the FDA is pursuing an Unapproved Drugs Initiative against as many as 3,000 drugs still on the market without approval. For many of these drugs still in limbo, a direct path to an NDA and possible marketing exclusivity may be obtainable.

Regulatory Challenges

A significant regulatory challenge to this process is determining exactly what additional or "bridging" data will be needed to support the proposed changes in the existing or previously approved drug. Since this is determined on a case-by-case basis, sponsors benefit in getting advice from regulatory professionals experienced in the 505(b)(2) approval route, as well as from the involved FDA review division.

Concerns About Safety

The 505(b)(2) pathway does not absolve sponsors and research organizations from preparing a detailed and carefully thought out development program. This must be done to anticipate and address likely regulatory concerns.

Approval Without an IND

In 505(b)(2) drug development, sponsors are often studying the Bioavailability/Bioequivalence (BA/BE) of a test drug versus a Reference Listed Drug (RLD) as part of the process. Because of this, it can sometimes be confusing to sponsors as to whether an IND is required.

An IND is required when a drug is involved in

a clinical investigation that is not exempt from the regulations. Guidance recently issued by the FDA gives greater clarity to what is a "drug," what is a "clinical investigation" and which clinical investigations are exempt for the IND process.

Because most drug development activity is undertaken with commercialization in mind, regulatory approvals without an IND are rare. In a few cases, the new product approval is based on the literature and the only study required is a Phase I bridging study to compare the systemic levels between the proposed drug product and the reference product. Done properly, these studies allow a company to reference the safety and efficacy information that is already known for the original drug and proceed directly to NDA submissions.

Affect on CMC

The CMC (chemistry, manufacturing and controls) section often comes into play in a 505(b)(2) submission because the formulation, components or API have been altered and the impact of any of these changes must be evaluated in terms of the safety and efficacy of the proposed drug product. However, a review of the evolution of the formulation and the data supporting the comparability of the different formulations, along with a CMC bridging study, can usually form the basis for the pharmaceutical development section.

Taking care to review the implications of changes during the development process and incorporating prudent comparability protocols at the right point in the program can provide the coherent pharmaceutical development summary needed for approval.

The Growing Importance of 505(b)(2) Today

In the relatively few years since clearing legal hurdles for 505(b)(2), the process has rendered significant changes on the drug development landscape. Today, as the patents for many blockbuster drugs and perhaps 100 other protected drugs are set to expire, smart marketers

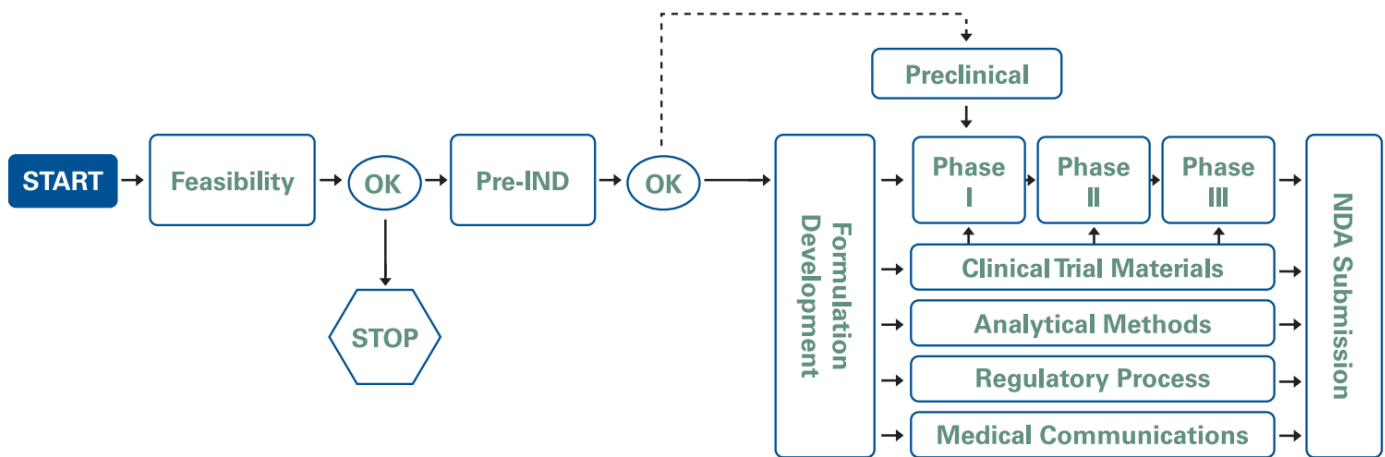
are seeking ways to create new differentiated products, new market niches and marketing exclusivity through 505(b)(2) development programs.

This path allows a sponsor to get out of 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.

Additionally, the 505(b)(2) process can be more attractive to investors because the product differentiation can provide significantly better market potential.

For many researchers and companies, 505(b)(2) offers a clear path to a differentiated product and some period of marketing exclusivity. The rising tide of drugs approved under this strategy is testament to its growing importance in the drug development market.

505(b)(2): Is It for You?



About Camargo Pharmaceutical Services

Camargo Pharmaceutical Services is the most experienced global strategist providing comprehensive drug development services specialized for the 505(b)(2) approval pathway and global equivalent processes. By assessing the scientific, medical, regulatory and commercial viability of product development opportunities, Camargo systematically builds and executes robust development plans that align with business strategies and ensure FDA buy-in every step of the way. Routinely holding three to six pre-IND meetings a month, Camargo works with product developers across more than 35 countries.



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