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What is 505(b)(2)?

The 505(b)(2) new drug application (NDA) is one of three U.S. Food and Drug Administration (FDA) drug approval pathways and represents an appealing regulatory strategy for many clients. The pathway was created by the Hatch-Waxman Amendments of 1984, with 505(b)(2) referring to a section of the Federal Food, Drug, and Cosmetic Act. The provisions of 505(b)(2) were created, in part, to help avoid unnecessary duplication of studies already performed on a previously approved – "reference" or "listed" – drug; the section gives the FDA express permission to rely on data not developed by the NDA applicant.

A 505(b)(2) NDA contains full safety and effectiveness reports but allows at least some of the information required for NDA approval, such as safety and efficacy information on the active ingredient, to come from studies not conducted by or for the applicant. This can result in a much less expensive and much faster route to approval, compared with a traditional development path, such as 505(b)(1), while creating new, differentiated products with tremendous commercial value.

The regulatory pathways at a glance

505(b)(1) NDA	505(b)(2) NDA	505(j) ANDA
Full application – Data predominantly obtained from studies conducted by and for the sponsor	Hybrid between an ANDA (505(j)) and full NDA (505(b)(1))	Appropriate for drug products that are the same as approved products

Drug candidates with 505(b)(2) potential

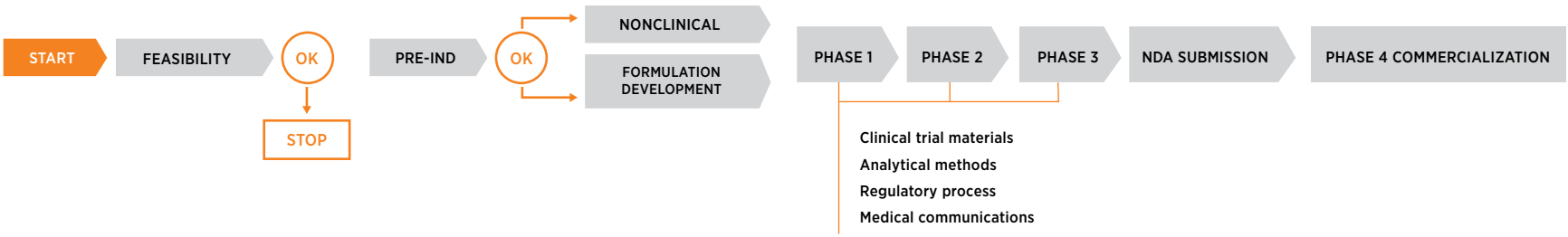
A company may wish to create a new dosage form that is faster acting, combines two active ingredients in a novel way, or provides a route of administration or mechanism of drug delivery that patients or doctors prefer over previous versions. Also, a company may wish to seek approval for a new indication for an already-approved drug or carry out an Rx-to-OTC switch. Such new products often contain well-understood active ingredients that are present in existing, approved drug products, reference drugs; so, companies must only create a bridge between what is already known about the previously approved reference drug and the novel drug product or indication. The 505(b)(2) NDA pathway makes this possible. In Europe, a regulatory approval route similar to the 505(b)(2) pathway is the hybrid procedure based on Article 10 of Directive 2001/83/EC.

Benefits of 505(b)(2)

505(b)(2) is particularly valuable for pharmaceutical and generics companies looking to alleviate competitive forces in their environments while still wanting to benefit from a development process that eliminates most nonclinical studies as well as extensive safety and efficacy tests.

- Relatively lower risk because of previous drug approval
- Lower cost, accelerated development due to fewer studies
- May qualify for three, five or seven years of market exclusivity

Navigating the 505(b)(2) approval pathway



Start:

Candidate identification
While the 505(b)(2) pathway offers a unique opportunity for rapid approval, success hinges on identifying products that have documented market differentiation, low development risk, and high-profit potential.

Ideal 505(b)(2) candidates include:

- Drugs with new indications
- Drugs with changes in dosage form, strength, formulation, dosing regimen, or route of administration
- New combination products
- Prodrugs of an existing drug
- In some cases, drugs with new active ingredients

Potential types of 505(b)(2)s include:

- Branded generics
- DESI drugs
- Prodrugs
- Orphan drugs
- Drug-device combinations

Biological therapeutics, so-called biosimilars, are not suitable for approval under the 505(b)(2) pathway.

Feasibility:

Candidate Assessment
Predevelopment assessment of candidates is essential to establish the value proposition of a product concept for investors and to reduce the risk of costly errors. To build evidence that will substantiate a product's potential value, the following questions must be considered:

Product Planning
"Traditional" new drug development and approval – generally required for a new chemical entity drug that has not been approved before or that doesn't have a significant marketing history in the U.S. or elsewhere – takes place under the provisions of section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act. When it comes to 505(b)(1), the passage from "promising molecule" to "approved drug" is long, difficult, risky, and expensive. Typically, achieving drug approval under the 505(b)(1) pathway – which requires the completion of new studies to establish the safety and efficacy of the drug in a specified disease or condition – can cost the sponsor up to 15 years and a billion dollars. Because a 505(b)(2) product can rely in part on the FDA's previous findings on the safety and efficacy of an active ingredient as well as data available in the public domain, at this product planning stage a potential developer of a 505(b)(2) should seek ways to weave such existing data into the product's development strategy to reduce its size, scope, timeline, and therefore cost.

In addition to representing a faster, less expensive path to market, products approved under the 505(b)(2) pathway can also sometimes qualify for several types of market exclusivity such as orphan drug exclusivity at seven years, new chemical entity exclusivity at five years, "other" exclusivity at three years for a "change" if certain criteria are met, and pediatric exclusivity at six months added to existing patents/exclusivity.

The accelerated path to approval and prospect of exclusivity make 505(b)(2) a cost-effective and commercially attractive route, but one with key differences from traditional 505(b)(1) development.

Scientific Viability

Does the science make sense? For instance, is the formulation stable and readily prepared? Is manufacturing scalable? Are active and inactive ingredients available and affordable?

Medical Viability

Does the product have a clear niche in the medical specialty? Is it effective for solving a unique problem or solving a problem in a unique way? Does it present an acceptable risk/benefit? Is there evidence the product would be appealing to the proposed patient population?

Regulatory Viability

What clinical trials or other data will be required to gain approval? Can development be expedited? Would exclusive marketing rights ("exclusivity") be available? What distinguishing information can be presented on the labeling for eventual promotional activity?

Commercial Viability

Is there a viable market for the product? What is the potential for future competition or substitution? What is needed to ensure reimbursement? What is the optimal pricing?

Pre-IND:

The 505(b)(1) pre-investigational new drug (pre-IND) development process is fairly straightforward:

1. Conduct required nonclinical – animal – pharmacology, pharmacokinetics and toxicology studies; carry out early pre-formulation studies and select a lead formulation to advance; develop appropriate analytical methods; gather stability data on the active ingredient and the dosage form; and develop a proposed clinical protocol;
2. Complete a pre-IND consultation with the FDA in which the sponsor presents findings from its nonclinical studies and manufacturing and analytical data, as well as a proposed clinical trial, in order to gain FDA agreement to move to human testing; and
3. File the investigational new drug (IND) application.

Compared to 505(b)(1), the 505(b)(2) process differs greatly. Here's how:

- **The order of the steps:** The 505(b)(2) process begins with the pre-IND meeting with the FDA, then moves to formulation development, and studies, if necessary, and then to the IND filing.
- **The goals of the pre-IND meeting:** For a 505(b)(2) product, pre-IND strategy is different than for a 505(b)(1). In proposing a 505(b)(2) development strategy in a pre-IND meeting, the objective is to gain FDA input and concurrence with the studies, with the chemistry, manufacturing, and controls (CMC) strategy, and with clinical research plans in a way that minimizes the number of new studies required. For many companies, obtaining FDA buy-in and successfully activating an IND are critical steps for securing investments.
- **The number and type of studies required:** Since the 505(b)(2) pathway allows the use of public data or the FDA's previous findings in lieu of novel trial data, some development programs may conduct bridging studies that preclude the need for nonclinical or clinical studies, or both.
- **Timing of CMC work:** For a 505(b)(2) product, the clinical trial materials for Phase 1 studies – often demonstrations of clinical bioequivalence – must be representative of the commercial manufacturing process, including packaging. In general, the three stability batches that will be used for shelf-life determinations are also prepared at this time. As a consequence, a good deal of CMC work must be invested prior to initiating even Phase 1 studies.
- **Timing of studies:** Because 505(b)(2) development plans rely largely on pre-existing data, and clinical studies can often be started simultaneously and developed in parallel, overall time to market is significantly shortened.

Together, these differences represent a formidable multifaceted challenge. When mishandled, the early steps of 505(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.

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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.

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