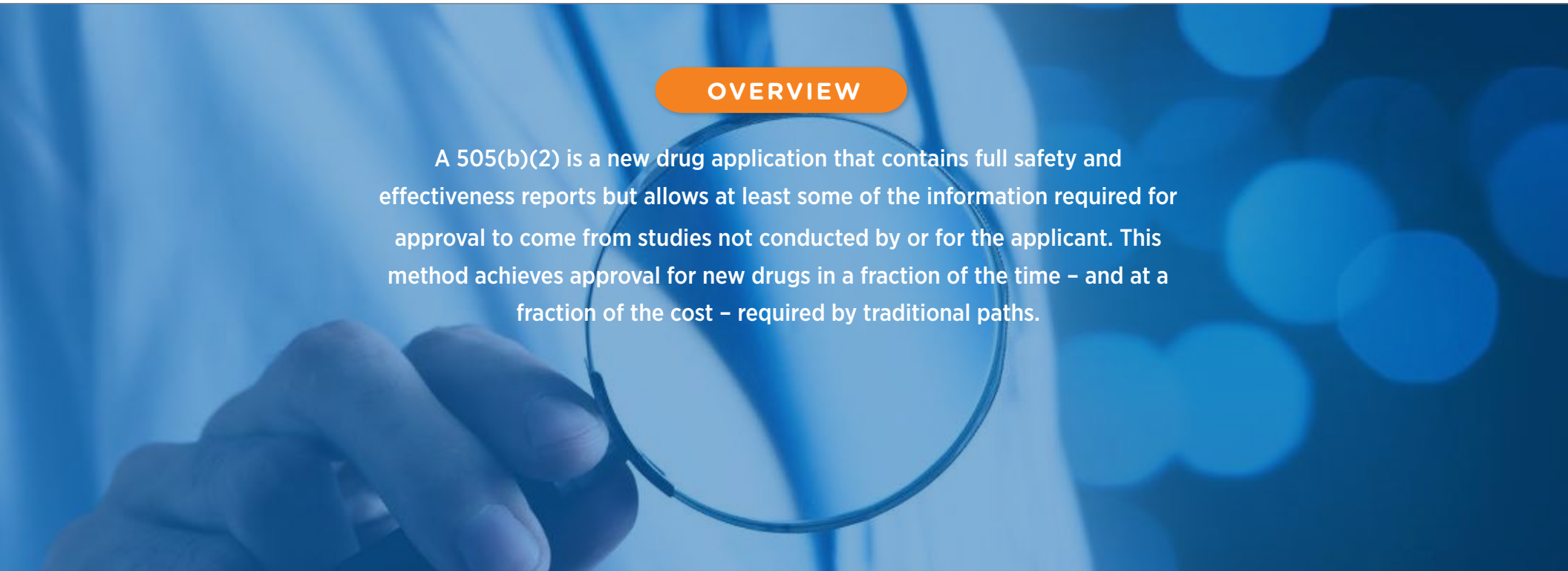
WHITE PAPER

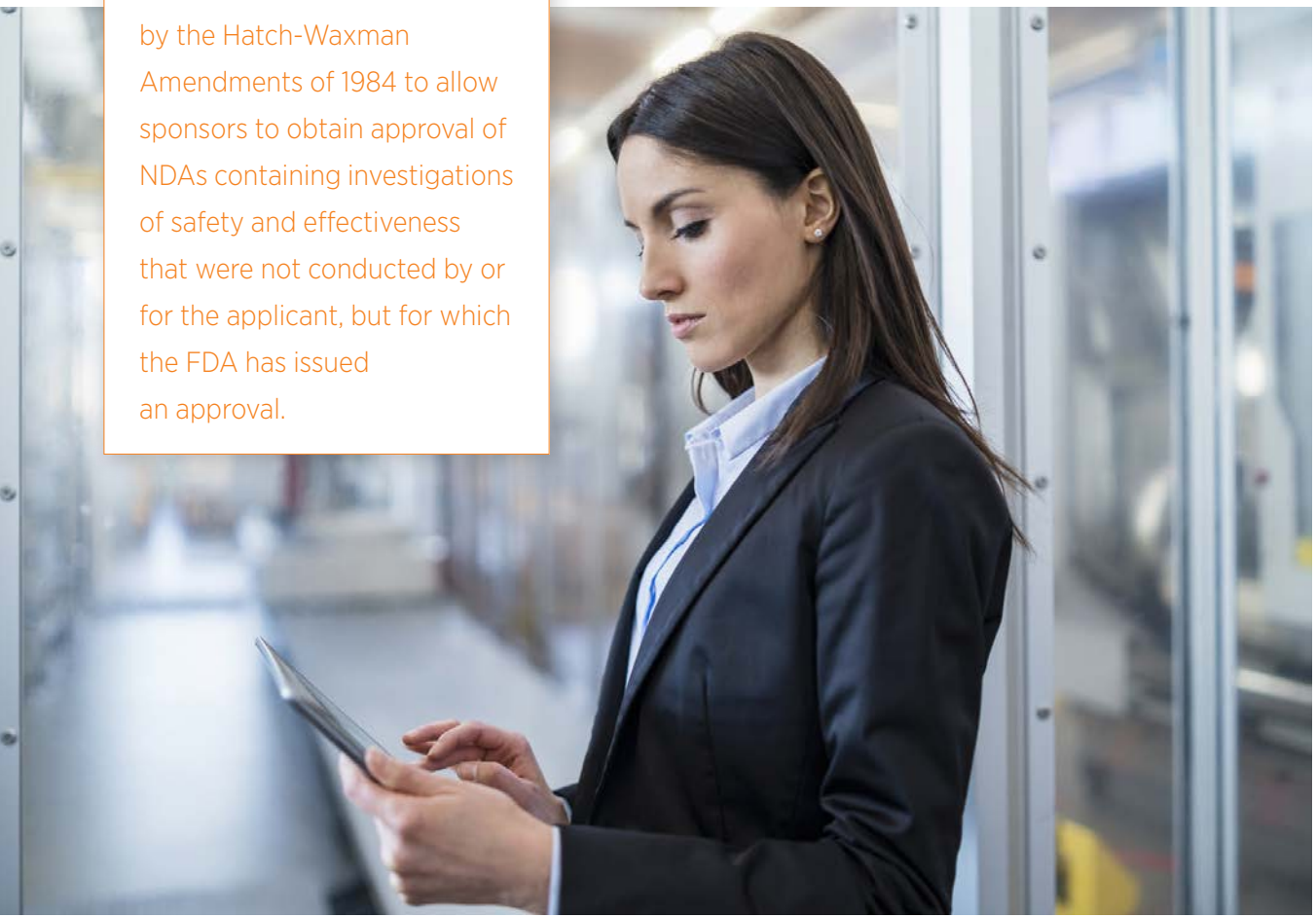
Understanding the 505(b)(2) Approval Pathway



OVERVIEW

A 505(b)(2) is a new drug application that 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 achieves approval for new drugs in a fraction of the time – and at a fraction of the cost – required by traditional paths.

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.



In 2006, about 20 percent of new small-molecule drugs were approved through the 505(b)(2) process; today, the figure is about 60 percent. 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, reducing costs and shortening development time. And while generic drugs approved under Section 505(j) may enjoy market exclusivity for only 180 days, a 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.

✓	Relatively low risk because of existing safety and efficacy information
✓	Lower cost due to the smaller scope and number of potential studies
✓	Increased speed because fewer studies are required

Potential regulatory pathways for drug products under development

505(j) ANDA	Appropriate for drug products that are the same as approved products
505(b)(2) NDA	Hybrid between and 505(j) ANDA and a full 505(b)(1) NDA
505(b)(1) NDA	"Full" application — data drawn predominately from studies conducted by the sponsor

Figure 1: Pathways for drug products

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 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 most 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 make small modifications, often significantly advancing the medication for patients' benefit.

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.

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.

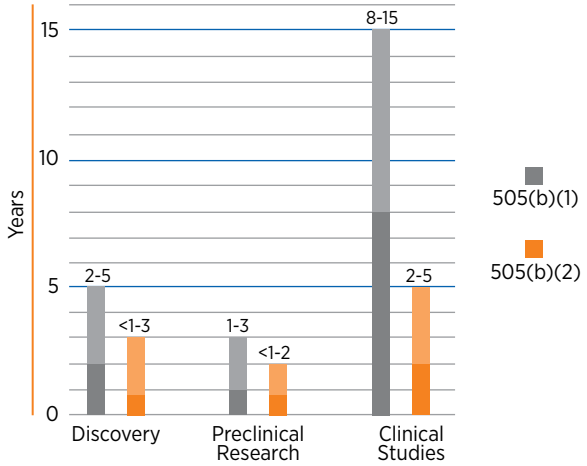


Figure 2: Drug development timelines

In the relatively few years since it cleared legal hurdles, the 505(b)(2) process has rendered significant changes to the drug development landscape. Today, smart marketers are seeking ways to create new differentiated products, new market niches, and marketing exclusivity through 505(b)(2) development programs.

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 by getting advice from regulatory professionals experienced in the 505(b)(2) approval route and 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 of a test drug versus a reference listed drug. Because of this, sponsors may be unsure if an investigational new drug (IND) application 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 about 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 1 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 submission.

Effect on CMC

The CMC (chemistry, manufacturing, and controls) section often comes into play in a 505(b)(2) submission because the formulation, components, or active pharmaceutical agreement 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 of 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.

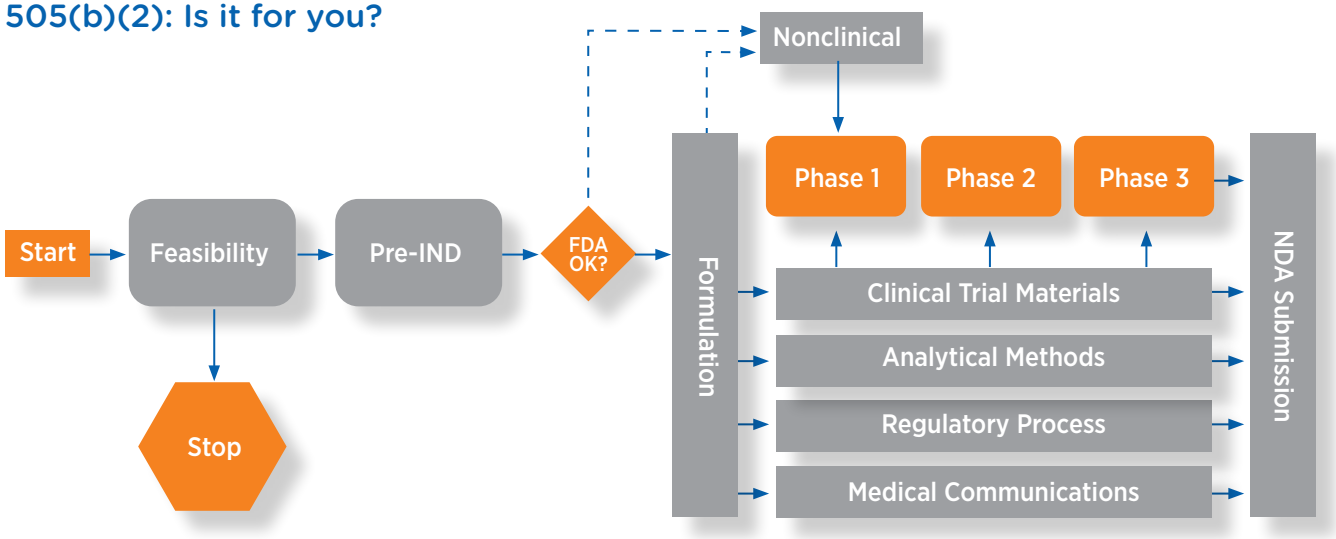
The growing importance of 505(b)(2) today

In the relatively few years since it cleared legal hurdles, the 505(b)(2) process has rendered significant changes to the drug development landscape. Today, 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 and extensive safety and efficacy tests, dramatically reducing costs and time to market.

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?



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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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