WHITE PAPER

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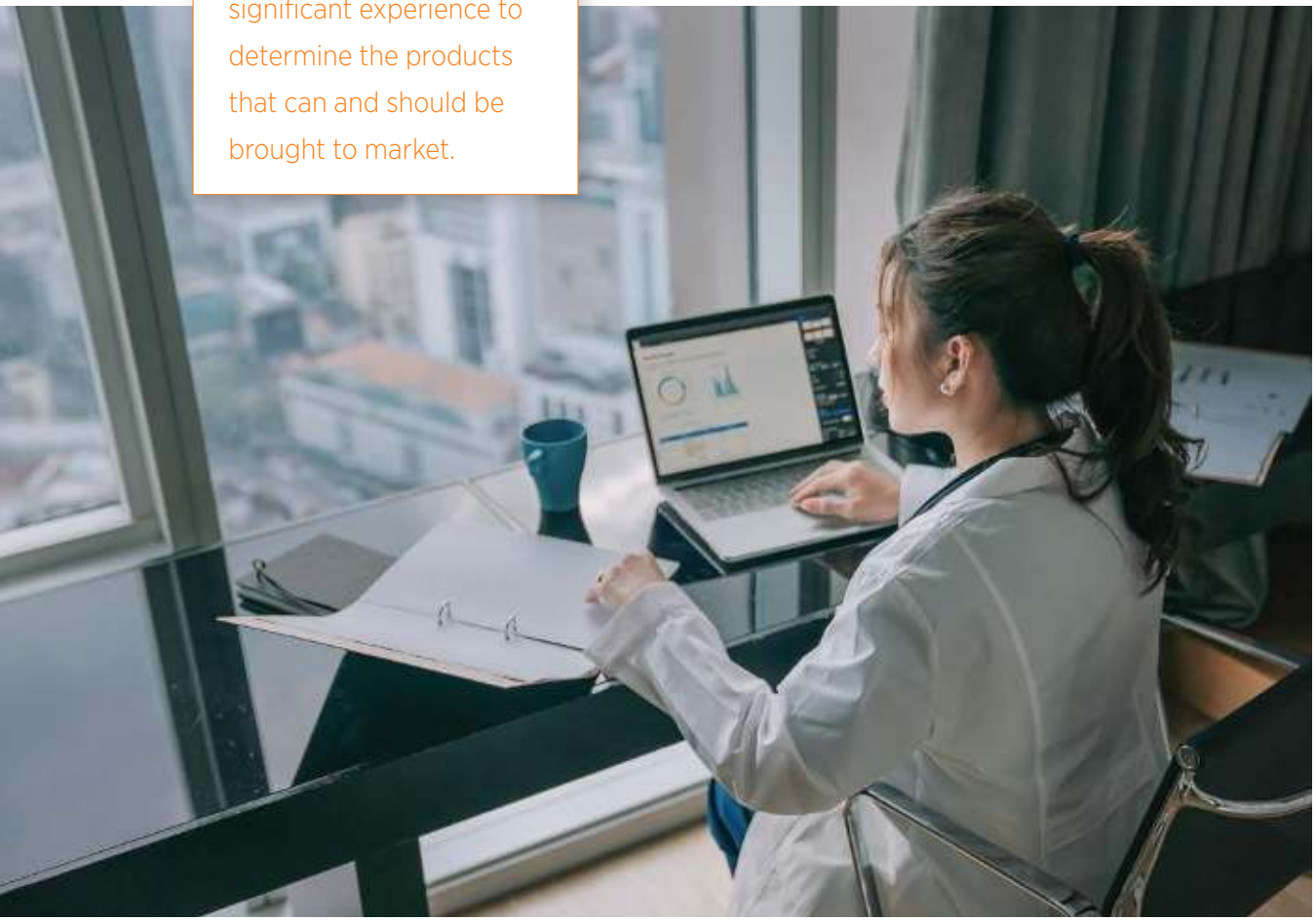
REGULATORY

Why More Drugs Than Ever Are Approved Through 505(b)(2)

OVERVIEW

Bringing a modified version of an existing drug to market through 505(b)(2) can offer a clear path to approval, a differentiated product, and at least some period of marketing exclusivity.

It takes a company with significant experience to determine the products that can and should be brought to market.



Introduction

Discovering and developing safe and effective new medicines is a long, difficult, and expensive process. Typically, a new drug application (NDA) approved by the Food and Drug Administration (FDA) under the standard 505(b)(1) regulatory path has taken as much as 15 years and a nine-figure investment. However, drugs approved under 505(b)(2), which can rely in part on data from existing reference drugs, can achieve FDA approval in as little as 30 months with only a fraction of the number of required clinical trials and much lower cost.

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 exclusivity, depending on the extent of the change to the previously approved drug and the type of clinical data included in the NDA.

Granted, 505(b)(2) is not right for every situation. A breakthrough compound with a broad demographic application and a novel therapeutic mechanism will have to take the long way around to be approved. However, there is a wide range of drug candidates with good market possibilities that have an opportunity for rapid approval under 505(b)(2). For drugs that represent a limited change from a previously approved drug, using data from studies in the public domain greatly shortens the development timeline. Opportunities include:

- New indications
- Changes in dosage form, strength, formulation, dosing regimen, or route of administration
- New combination products
- New molecular entities (new active ingredients)
- Prodrugs of approved drugs

When you compare the return on investment, the best bottom-line strategy for many pharmaceutical, biotech, and generic companies is to seek opportunities in niche markets to make new use of compounds already available.

Knowing which products are viable and have adequate long-term market potential is a common development challenge and a good reason to select a contract research organization with experience in 505(b)(2).

The long way around

Why is a typical 505(b)(1) drug development program so costly?

Before a drug company or research institution can submit an investigational new drug (IND) application to the FDA, it completes or conducts an average of six and a half years of basic discovery work and preclinical testing. This includes:

- Toxicology, including tests to determine gross pathology and effect, mutagenicity, and dose selection
- Preformulation to characterize the molecule and to design an optimum drug delivery system
- Formulation studies to identify and quantify the active compound and test it for physical and chemical stability
- Pharmacokinetics, which determines the absorption, distribution, metabolism, and excretion of the compound *in vivo*

Once preclinical testing is complete, a company files an IND. If the FDA agrees that the discovery and preclinical tests indicate that the compound will be relatively safe to test in humans, the agency will approve the application and allow the sponsor to ship the unapproved drug through interstate commerce.

No wonder they call them trials

At this stage, the sponsor can consider clinical trials. This process begins with the development of a protocol that describes the people who will participate in the trial, the schedule of tests and procedures, the drug and dosages to be used, and the length and goals of the study. Clinical trials cannot begin until the final trial protocols have been reviewed by a local institutional review board with a panel of scientists and nonscientists from hospitals and research institutions.

Phase 1, or first-in-human, trials primarily concern toxicity testing. The drug is administered to 20-80 healthy volunteers to determine probable safe dosages and side effects and to learn how the drug is metabolized and excreted.

If the compound survives Phase 1 – and only about 40 percent do – Phase 2 studies can begin. In this stage, the drug is administered to volunteer patients to determine effectiveness. This phase typically takes about two years. Only half of the drugs that make it through Phase 1 survive Phase 2.

Out of 100 drugs entering Phase 1 trials, only about 20 survive to this point. If evidence of effectiveness is demonstrated in Phase 2, the drug is given to 1,000 to 5,000 volunteer patients in Phase 3, a phase that can last as long as three and a half years.

About seven years have elapsed and several hundred million dollars have been spent before the sponsor is finally able to submit an NDA to the FDA. The application will include all animal and human data, analyses of the data, information on how the drug acts in the body, and information on the chemistry and manufacturing of the drug. Applications with an excess of 100,000 pages of data are not uncommon.

Although only a handful of the drugs that enter clinical testing are eventually approved by the FDA, the cost of all those tests and clinical trials for the failed candidates must still be considered part of the overall cost of developing drugs.

> Among other advantages, the 505(b)(2) pathway offers a way to mitigate exposure to costly failures.

The 505(b)(2) advantage

For many years, the FDA had an informal policy to review and approve NDAs based solely on literature. These “paper NDAs” also were used for copies of approved drugs, called generics, which, at the time, lacked formal approval requirements.

That changed in 1984 when Congress passed the Drug Price Competition and Patent Term Restoration Act, known as the Hatch-Waxman Amendments. This act set forth the process by which marketers of generic drugs can file abbreviated new drug applications (ANDAs) and codified the paper NDA under 505(b)(2).

Regardless of the regulatory pathway chosen for approval of an NDA, the FDA standards for the demonstration of efficacy and safety are the same; it is only the source of information that differs between the two paths. This underscores the necessity of working with an industry expert in 505(b)(2) approvals.

An expert understands what constitutes sufficient evidence – and therefore which specific studies can be replaced by existing data for each individual compound.

When information may suffice

At times, existing data may prove that the drug's known effectiveness can be applied to a new population or to a different dose, regimen, or dosage form. The effectiveness of a new product may be adequately demonstrated without any additional clinical efficacy trials. These situations include:

Pediatric: Regulatory agencies must conclude that the course of the disease and the effects of the drug are sufficiently similar to permit extrapolation from adult efficacy data to pediatric patients. Evidence may include common pathophysiology of the disease, common drug metabolism, and experience with other products in the drug's therapeutic class.

Bioequivalence: Alternative formulations and new dosage strengths may be assessed on the basis of evidence of bioequivalence.

Modified-release dosage forms: In some cases, modified-release dosage forms may be approved on the basis of pharmacokinetic data linking the new dosage form to an approved immediate-release dosage form.

Different doses, regimens, or dosage forms: Where blood levels and exposures are not very different, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data alone.

In addition, a single clinical study of a new use, when combined with independent substantiation from study data in related uses, can often provide adequate evidence of effectiveness in different doses, regimens, or dosage forms; in other phases of the disease or closely related diseases; and in other populations.

Fosamax is a good example of how this works. Fosamax had been demonstrated to reduce the risk of hip and spine fractures in postmenopausal women with osteoporosis.

In 2005, the FDA approved a new product – Fosamax Plus D, which added the benefit of a weekly dose of Vitamin D – with a single pharmacokinetic study along with supporting documentation under 505(b)(2).

A change in the landscape

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. Additionally, the 505(b)(2) process may be more attractive to investors because, in addition to up to seven years of market exclusivity, the product differentiation can provide significantly better market potential.

Conclusion

Bringing a modified version of an existing drug to market through 505(b)(2), although potentially much faster and less costly than starting with a new compound, is a demanding process that requires thorough understanding of the FDA and how it works. In 2020, 505(b)(2) approvals accounted for 60 percent of NDA approvals granted by the Center for Drug Evaluation Research, representing important advances in patient care across a wide range of therapeutic areas.

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

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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