



White Paper

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



Discovering and developing safe and effective new medicines is a long, difficult and expensive process. Typically, a new drug application 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 to work its way through the system. However, drugs approved under 505(b)(2), which can rely in part on data from existing reference drugs, can be developed and achieve FDA approval in as little as 30 months with only a fraction of the number of required clinical trials and at a much lower cost.

Additionally, 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 extent of the change to the previously approved drug and the type of clinical data included in the New Drug Application (NDA).

Granted, 505(b)(2) is not right for every situation. A breakthrough compound with a broad demographic application and a novel therapeutic mechanism may have fabulous market potential, but it will have to take the long way around to be approved. However, there are 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, utilizing 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

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



pharmaceutical, biotech and generic companies is to seek opportunities in niche markets in order 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 specialist in 505(b)(2) like Camargo.

### 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 Application (INDA) 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 both 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 the discovery and preclinical tests indicate the compound will be relatively safe to test in humans, then the FDA will approve the application and allow the sponsor to ship the unapproved drug in 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 I or first-in-human trials primarily concern toxicity testing. The drug is administered to 20 to 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 I — and only about 40 percent do — Phase II 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 I survive through Phase II.

Out of 100 drugs entering Phase I trials, only 20 remain. If evidence of effectiveness has been

demonstrated in Phase II, the drug is then given to 1,000 to 5,000 volunteer patients in Phase III, 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 manufacture 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” were also 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 one chooses 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 drugs in this 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; other phases of the disease or closely related diseases; and other populations.

Fosamax is a good example of how this works. Fosamax had been demonstrated to reduce the risk of both 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 clearing legal hurdles, the 505(b)(2) process has rendered significant changes on the drug development landscape. Today, as the patents for many blockbuster drugs 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 companies 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 may be more attractive to investors because, in addition to up to seven years of market exclusivity, the product differentiation can provide a significantly better market potential.





## Summary

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 still a demanding process that requires thorough understanding of the FDA and how it works. In fiscal year 2006, approximately 20 percent of new drugs were approved through the 505(b)(2) process. According to data for the current year, the percentage of new, small-molecule drugs approved has exceeded 80 percent or more.

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.

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## 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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