

The 505(b)(2) Drug Development Pathway:

When and How to
Take Advantage of a
Unique American
Regulatory Pathway



The 505(b)(2) regulation offers a less expensive and faster new drug development pathway that may be particularly attractive to a manufacturer with experience in developing generic products. It involves making significant changes to an existing product approved by the US Food and Drug Administration (FDA), called the reference product, to create a new drug with its own indication, formulation, target population and/or other differences that need to be supported with clinical studies. A major advantage of this pathway is that it allows a sponsor to rely, at least in part, on FDA's findings of safety and/or effectiveness for the previously approved drug, thereby reducing the number of clinical trials required for approval. Another incentive is three to five years of market exclusivity for 505(b)(2) products, depending upon the extent of changes to the reference product and the type of clinical data included in the approved New Drug Application (NDA).

However, like all drug development strategies, the 505(b)(2) pathway requires careful consideration and planning. Important issues to consider include intellectual property concerns, the amount and quality of supporting information available from reference products or the literature, the logistics of conducting clinical trials with generic-like products, market competition for approved products and requirements for an international product launch. Here we discuss practical strategies for drug development via the 505(b)(2) regulatory pathway.

Drugs Can be Approved via One of Three Regulatory Pathways

New drug products can belong to one of two broad categories: brand new drugs and identical or close copies of previously approved drugs, also called generics. Globally, separate regulatory pathways for innovator products and generic drugs are well established. US regulations, however, divide these drugs into three categories: (1) new drugs, covered under Section 505(b)(1) of the *Food, Drug, and Cosmetics Act (FD&C Act)*; (2)

generic drugs, covered under Section 505(j) of the *FD&C Act*; and (3) "similar" drugs, covered under Section 505 (b)(2). It is the third category that is discussed here.

The generic and 505(b)(2) categories were added by the *Drug Price Competition and Patent Term Restoration Act* of 1984, usually referred to as the *Hatch-Waxman Act*. The *Hatch-Waxman Act* aimed to promote generics while leaving intact a financial incentive for new product research and development. It was an attempt to balance the need for innovation with the desire for lower-cost alternatives within a reasonable length of time. Drug companies were given the opportunity to create not only exact copies of previously approved drugs, provided there was no infringement of patents, but also improved versions of previously approved drugs by updating formulations or finding new uses. **Table 1** describes the three pathways under the *FD&C Act*.

Despite existing for more than 25 years, along with generic drugs, the 505(b)(2) products have only recently become popular with drug companies due to increased challenges to discover and develop new chemical entities. As with innovator drugs, products following the 505(b)(2) pathway are subject to the full user fee under the *Prescription Drug User Fee Act (PDUFA)*. They also may require several clinical and nonclinical studies that could involve significant resources, albeit less than for an innovator product but much higher than for a generic drug. Some key parameters for the three product categories are listed in **Table 2**.

The 505(b)(2) Pathway is Unique to the US

The 505(b)(2) application is intended to encourage sponsors to develop improved generics, i.e., drugs similar to an approved product with some significant changes that are not permitted under Abbreviated New Drug Application (ANDA) rules. The 505(b)(2) pathway replaced the "Paper NDA" pathway used prior to the *Hatch-Waxman*

Table 1. Regulatory Pathways for New Drug Products

505(b)(1) NDA	New drug	Requires extensive clinical and nonclinical studies to demonstrate the safety and efficacy of a given drug for the target indication. Due to the amount of data required to support the application, such NDAs could take many years and require an enormous allocation of resources.
505(j) ANDA	Generic drug	An abbreviated application containing only bioavailability/bioequivalence (BA/BE) studies comparing the proposed product to the innovator product.
505(b)(2) NDA	New drug containing similar active ingredient as a previously approved drug	Modified version of a previously approved product that requires additional clinical and nonclinical studies, other than BA/BE studies, to demonstrate safety and efficacy. This application differs from the typical NDA in that the sponsor can rely, at least in part, on FDA's findings of safety and/or effectiveness for a previously approved drug (the reference drug). Thus, a 505(b)(2) NDA can provide a shorter and less-costly drug development program and therefore bring a profitable drug to market more rapidly.

Table 2. Comparison Between Conventional NDA, ANDA and 505(b)(2) Drug Submissions

	NDA	505(b)(2)	ANDA
User Fee	Yes	Yes/No	Yes
Studies	Full	Partial	BA/BE
New Chemical Entity	Yes	No	No
New Ingredients	Yes	Yes	No
New Formulation	Yes	Yes	No
Patented	Yes	Yes	No
Market Exclusivity	5 years	3–5 years	0.5 years

Act, whereby FDA could approve NDAs that relied on published studies and lacked any reference to innovator safety and effectiveness data. Paper NDAs were frequently challenged by innovator product manufacturers, citing lack of sufficient safety and efficacy data. Under the 505(b)(2) regulation, FDA has the authority to approve new products based on fewer new studies to demonstrate their safety and efficacy and relying extensively on the agency’s previous findings of safety and efficacy for the reference product. The sponsor of a 505(b)(2) product is not required to obtain a right of reference from the innovator product manufacturer. However, the sponsor needs to include data from bridging studies to support changes from the reference drug.

As mentioned, the 505(b)(2) application applies when certain changes are made to the innovator drug to either create a new formulation or include new uses/indications. The following are examples of changes to approved drugs that would fall under the 505(b)(2) mechanism:

- changes in dosage form, strength, formulation, dosing regimen or route of administration
- new combination product, including substitution of an active ingredient
- modified active ingredient (e.g., salt, chelate, ester, complex, etc.)
- new indications for previously approved drugs
- over-the-counter switch of an approved prescription drug

Because 505(b)(2) products are considered new products, they are subject to the *PDUEA* user fee requirement. Review by FDA is similar in duration to that of traditional NDAs, and the approved product is eligible for a minimum of three years of market protection from generics if the bridging studies were other than bioavailability (BA) and bioequivalence (BE) studies. This regulatory process is unique to the US. Products approved under the 505(b)(2) pathway typically are approved either as generics or new products in other countries.

The 505(b)(2) Pathway Offers Many Advantages to Manufacturers and Patients

There are advantages for all stakeholders from developing 505(b)(2) products. This pathway eliminates duplication of experiments and encourages developers to conduct new studies that add value to the final product, such as a better understanding of mechanisms of action, improved formulation and utilization of the same product for multiple diseases. Also, development of such products creates new intellectual property while protecting the rights of the original product, and providing a fair incentive for the investment. Since 505(b)(2) products are derived from reference products for which extensive safety and efficacy information is available, they generally carry less risk, cost less and can achieve FDA approval in a much shorter time. Some 505(b)(2) products have been created with less than \$30 million in additional investment (in terms of new clinical and nonclinical studies conducted) and in about three years, which is remarkable compared to the cost and timeline for a traditional new drug.

Perhaps the biggest incentive to develop 505(b)(2) products is the three to five years of market exclusivity in the US, depending upon the extent of changes to the previously approved drug and the amount of data submitted to FDA. This is an apparent advantage when compared to ANDA approval, where exclusivity can be held for only 180 days and applies only to the first generic product. **Table 3** lists the different terms of market exclusivity available by product category and target indication.

Market exclusivity enables manufacturers to take advantage of greater pricing flexibility. During the market exclusivity period they can promote their product over the innovator drug and build their own brand with an attractive price without fear of price erosion due to generic competition. Most importantly, 505(b)(2) products may receive an “AB” substitutability rating in the Orange Book. Thus, from a therapeutic substitution perspective and under state formulary laws, the 505(b)(2) product is not at a disadvantage relative to a generic drug.

Table 3. Market Exclusivity Available to FDA-Approved Products

New Chemical Entity	5 years
New Product (formulation or indication)	3 years
Orphan Drug designation	7 years
Pediatric Drug designation	6 months

Challenges for Developing 505(b)(2) Drug Product

There are some unique challenges facing 505(b)(2) applications. They often require substantial additional innovative work to bring the product to market. Since similars involve significant changes to the reference product formulation, either by including additional components or making changes to the active pharmaceutical ingredient, the impact of these changes on safety and efficacy must be evaluated via clinical and/or nonclinical studies. Such studies could uncover new issues, leading to further investigations and associated costs. Also, unlike generic drugs, such products involve extensive interactions with FDA to proactively understand regulatory, scientific and technical requirements. Such products are considered new and unique by FDA; hence, the review process is analogous to that for traditional NDAs.

Also, since portions of the 505(b)(2) application could utilize self-generated proprietary data, this information needs to be protected via a patent or trade secret agreement, as applicable. Still, significant portions of the information could be in the public domain in existing patents for the innovator product. Unlike the traditional NDA, wherein the sponsor owns all the data necessary for approval (or has obtained the right to reference), the filing or approval of a 505(b)(2) application may be delayed due to reference drug patent or exclusivity protection. Sponsors filing 505(b)(2) applications must include patent certifications in their applications and must also provide notice of certain patent certifications to reference drug NDA and patent holders.

Determining what additional information may be required for approval is a critical strategic requirement. Information requirements usually are subject to case-by-case determination by FDA. FDA guidance documents and discussions with regulatory professionals experienced in the 505(b)(2) approval route, as well as with the relevant FDA review division, are critical in understanding what data are necessary and adequate. The biggest risk: if the required studies are only BA/BE studies, the product will receive a 505(b)(2) designation and be subject to associated user fees (which are about \$1.4 million (US) in 2010) without being eligible for any market exclusivity and thus subject to generic competition from the beginning of market approval.

There are few additional challenges associated with the use of the 505(b)(2) pathway. These products face fierce competition from generics with similar biological properties and since they are more expensive than generics, a robust marketing campaign may be required to attract customer attention. On the other hand, 505(b)(2) products offer certain advantages over innovator and/or generic drugs, enabling the manufacturer to promote these benefits directly to patients. These could be marketing advantages such as a formulation that is easier for patients to take, extended dosage, different strength, etc.

Strategies for Developing 505(b)(2) Products

For small drug companies, the 505(b)(2) pathway for a new product could prove an attractive business model for the simple reason that it takes much less time, cost and risk to get the product onto the market compared to innovator drugs, and could yield significantly higher returns on investment compared to generic drugs.

A good strategy could mean the difference between a successful, i.e., profitable, and unsuccessful product. The following are key strategic considerations for a 505(b)(2) product:

- extent of innovation/modification made to the innovator product: these modifications decide whether the product is applicable for a 505(b)(2) review or not, and help determine the number of years of market exclusivity granted
- thorough analysis of available data: before embarking on manufacturing a 505(b)(2) product, a company should thoroughly analyze the data available, including the scientific basis of approval of the reference drug, published literature, particularly since the innovator drug was approved, market competition, etc. (The amount of available data previously submitted to FDA determines whether this is a viable project.)
- development strategy: careful analysis of data should lead to a list of the additional studies that may be required for a given 505(b)(2) product; bridging studies are required to show that changes to the innovator product lead to the desired impact on safety, efficacy and tolerance of the proposed drug product

- FDA discussions: there is no substitute for robust discussions with the relevant FDA review division regarding the proposed and executed development strategy; FDA offers significant advice regarding final requirements for an approval, and it has been statistically demonstrated that companies that involve FDA in discussions early in their product development plans and implement the agency's suggestions increase their chances for first cycle approval almost three-fold, leading to enormous time and cost savings and, hence, higher returns on investment
- implementation of strategy: exhaustive implementation planning is the path to success; timelines should be diligently observed and any deviations aggressively addressed
- cost control: cost incurred depends upon the preclinical and clinical studies required, amount of information available regarding the reference drug, advancements in analytical technology and various other such factors; bridging studies should be scientifically justified and strategically executed to control cost
- marketing and branding strategy: as 505(b)(2) products are generally more expensive than generic versions of the innovator drug, the manufacturer should have a robust marketing plan

Conclusion

Over the years, the 505(b)(2) regulatory pathway has become very attractive to companies of all sizes. It is the proverbial "low-hanging fruit" for manufacturers due to the short time of marketing with attractive returns on investment. Every year FDA approves about twice as many 505(b)(2) applications as traditional 505(b)(1) applications. It is projected that due to increased challenges in creating new products, 505(b)(2) products might comprise more than 70% of all FDA approvals within 10 years. This pathway is particularly attractive to manufacturers transitioning from generic drugs to innovator products. Due to the similarities to traditional drug development, these products offer a low-risk market entry point by training the work force in the traditional development processes. However, there are unique scientific, regulatory, logistical and financial challenges to developing such products—all of which could convert a potentially attractive project into a constant headache.

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