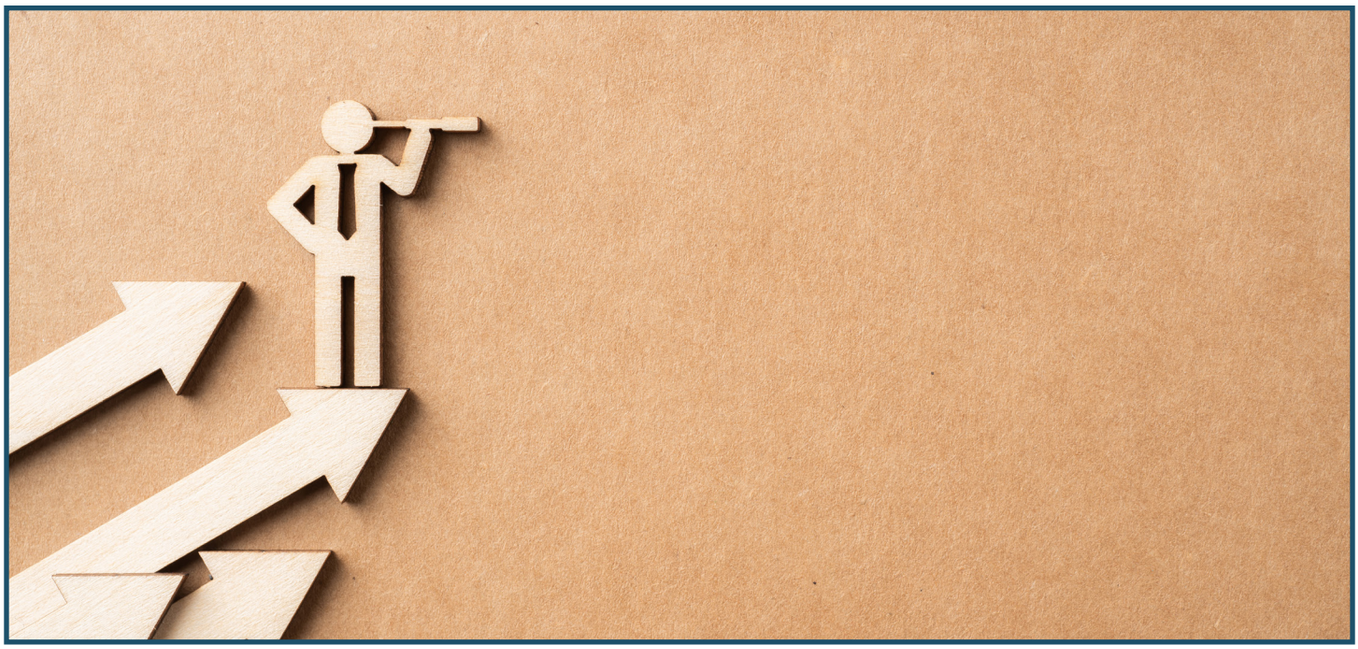

505(b)(1) and 505(b)(2) Pathways for New Drugs: When to Use & Common Misconceptions

A fundamental question for any drug development program is which regulatory pathway to pursue. The answer is important to determine early on, because it dictates the scope of clinical and nonclinical studies that need to be conducted and how the marketing application will be presented to regulators. It also heavily influences a host of other decisions from early development to approval.

As you consider your development pathway, you should start by asking yourself a few key questions:

1. Is the active ingredient(s) novel, or is it the same or very similar to another drug that has already been approved?
2. If the active ingredient is the same, is there a reference listed drug product (RLD)?
3. Are there other differences between your product and the approved product, such as the route of administration, that could impact safety or effectiveness?
4. Is your product being developed for the same indication as the approved drug?
5. Are there data from the approved product or published literature that you can rely upon to limit the need for (or scope of) your own studies?
6. If you rely on external data, how does that impact market exclusivity for you own product?

These are certainly not the only questions that need to be asked — far from it — but they do help illustrate one key point. Asking the right questions up front naturally leads to a cascade of other important considerations. The ability to ask the right questions, obtain accurate responses, and thoughtfully apply the information that you gather to your program provides a rational and deliberate approach to choosing an appropriate drug development pathway.

Choosing Between 505(b)(1) and 505(b)(2)

If you are familiar with drug development, then you have likely encountered the terms "b1," "b2," and maybe even "j" tossed around to describe certain drugs and programs. These abbreviated terms refer to specific parts of Section 505 of the Federal Food, Drug, and Cosmetic (FD&C) Act. These statutes describe applications to legally market a new drug in the United States.

As described in the statutes, all "new drug" applications submitted for marketing approval require "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use."

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If a drug is novel, meaning that the active ingredient has never been approved by the FDA, then development will follow the **505(b)(1) pathway**. Under 505(b)(1), all investigations supporting safety and effectiveness, both clinical and nonclinical, are conducted by or on behalf of the sponsor. These studies form the basis of evidence upon which approval is either granted or denied.

In some cases, sponsors may wish to apply for approval of a drug that constitutes a modification of a previously approved drug. This modification could be a reformulation, a different route of administration, dosage form, strength, and/or indication, or even a new prodrug or combination product involving the approved drug. For any of these, the development pathway will follow provisions under **505(b)(2)**. While a 505(b)(2) program still requires a full accounting of safety and effectiveness, it also allows for reliance on previous investigations. Meaning, investigations that were not conducted by or for the applicant/sponsor and for which the applicant/sponsor has not obtained a right of reference.

For both the 505(b)(1) and 505(b)(2) pathways, the sponsor submits a New Drug Application (NDA) to the FDA. If the FDA agrees that the sponsor has met the statutory requirements of safety and effectiveness for a new drug (including the adequacy of the manufacturing program), then the drug will be approved for marketing.

505(b)(2) Drugs – How to Bridge and What to Reference

While both 505(b)(1) and 505(b)(2) drugs require a full account of safety and effectiveness, the 505(b)(2) pathway provides added flexibility for how this requirement is met. The purpose for this flexibility is to reduce unnecessary testing and to provide a way for follow-on products to make it to market more quickly.

When thinking about a 505(b)(2) development program, the first question to ask is, how is your drug different from the approved drug? From there, you can determine what data you need to generate to "bridge" your drug to the approved drug. Sometimes, this could be as simple as demonstrating that the bioavailability of your drug matches, although is not necessarily bioequivalent to, that of the approved drug. Other times, the required studies may be much more involved and resemble what is essentially a full clinical program – early stage pharmacokinetics studies followed by larger mid- and late-stage efficacy trials.

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Beyond any required studies, a portion of the requirements for your 505(b)(2) NDA will be met by data that you did not generate or that you do not otherwise own. This often takes the form of FDA's previous findings of safety and effectiveness for the approved drug, which is contained in the drug's approved labeling (package insert). Published literature is another potential source of information that can be used to support the application.

Summary Basis of Approval

Can the Summary Basis of Approval (SBA) for the approved drug be used to support a 505(b)(2) NDA? This is a question that we often get from clients and one that even those who have been in drug development for many years can struggle with.

First, let's describe what the SBA is. The SBA (described in 21 CFR 314.430) is a summary of the safety and effectiveness data and information evaluated by the FDA during the drug approval process. SBAs, along with the separate discipline reviews (e.g., clinical pharmacology, toxicology, medical, statistical), are publicly available documents that contain a wealth of information about a drug's approval package.

This seems like an ideal document to cite as support for a marketing application, right? Not so fast. Unlike the approved product label, SBAs represent the opinions of individual reviewers and not the FDA's ultimate findings for the drug. As a result, you cannot rely on an SBA for the NDA. Despite this, an SBA is not without value to a 505(b)(2) development program, especially early in development.

One of the most common ways that information from an SBA is leveraged in a 505(b)(2) development program is to use it to support the initial Investigational New Drug Application (IND). Using safety information from the SBA of an approved drug, sponsors may be able to reduce or eliminate certain preclinical investigations (IND-enabling studies) and get into initial human studies more quickly.

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Potential Impacts on Market Exclusivity

When sponsors are considering their development pathway, questions often arise about market exclusivity. Market exclusivity is granted upon approval of a drug and establishes a period of time during which no other marketing applications can be accepted and/or approved for the same active ingredient.

For 505(b)(2) applications, market exclusivity is typically 3 years from the time of approval (Clinical Investigation Exclusivity, or CIE), rather than the typical 5 years for an innovator product. While this is true, it is important to recognize that market exclusivity is not actually tied to the development pathway (this is a common misconception).

In fact, 505(b)(2) drugs can have longer or shorter exclusivity durations. There are examples where 505(b)(2) drugs have been granted new chemical entity (NCE) exclusivity, which provid=es 5 years of market exclusivity, or even orphan drug exclusivity, which provides 7 years of exclusivity. For more information on this and other aspects of market exclusivity, please see our previous blog on the topic.

Conclusions

The 505(b)(2) development pathway provides far more efficient drug development for follow-on products by allowing reliance on certain external data and information for the NDA. Understanding how to bridge your drug to an approved drug and what types of information are appropriate to use is critical to getting your drug approved. While the development pathway does not dictate the length of market exclusivity, there are several other factors that do. Contact us to speak with one of our senior consultants about the 505(b)(2) pathway and how it can be used to get your drug to market faster and more efficiently.

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