505(b)(2) NDA: Navigating the regulatory pathway and the importance of strategic partnering

Review and Approval of new drugs by the Food and Drug Administration (FDA) is the foundation of drug safety in the United States. Despite this, a number of prescription and over the counter drugs are marketed in the US without FDA approval, often unbeknownst to the patients and health care providers who take and prescribe them. Typically, these are drugs that came to the market prior to the monumental 1962 Food and Drugs Act amendment and, for a variety of historical reasons, have not met the modern standard of scientific evidence for favorable risk/benefit established through this legislation. In recent communications, the FDA has made it clear that historical justifications for the marketing of unapproved drugs will no longer be accepted, and all currently marketed drugs must meet modern scientific and medical standards (1). It is the stated goal of the FDA to subject all marketed unapproved drugs to immediate enforcement action "at any time, without prior notice" (1).

For companies marketing unapproved drugs, the question is not whether enforcement will occur, but when will it occur. According to the FDA, the agency has removed numerous unapproved drug products from the market in 17 different drug classes since 2006 (2). To avoid enforcement action and possible removal from the market, the FDA is urging companies that market unapproved drugs to submit New Drug Applications (NDAs). Thus, the first step toward compliance is to understand the purpose, content, and evidentiary standards of the NDA.

The purpose of an NDA is to provide FDA reviewer(s) with enough information to reach the following key decisions (3):

- Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks;
- Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain;
- Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

In order for the FDA to make these determinations, the NDA must tell the marketed unapproved drug's entire story, including results of pre-clinical testing (animal studies), results of clinical testing (human studies), information on structure and composition, how the drug behaves in the body, and how it is manufactured, processed and packaged.

Sponsors of marketed unapproved drugs must determine the most economical path for NDA approval based on the ability to leverage all available supportive data. This data need not come solely from studies conducted by the applicant holder. Instead, the marketed unapproved drug's clinical history must be taken into account along with the regulatory status and composition of relevant reference drugs and the quality/quantity of available published and sponsor derived data.

Depending on the evidence available, the sponsor may file one of the following NDA types:

- 505(b)(1): this application is used for approval of new drugs whose active ingredient has not previously been approved. Because such a drug would typically have no clinical history to

reference outside of the sponsor development program, extensive data derived by or for the sponsor demonstrating safety, efficacy and quality are required (Figure 1 below). For reasons of time and cost, this application type would not typically be used by a sponsor of a currently marketed unapproved drug.

- 505(j)/Abbreviated New Drug Application (ANDA): this application relies on data from an approved reference drug application and does not require the sponsor to generate preclinical and clinical data to establish safety and effectiveness. Thus, the sponsor needs only to demonstrate bioequivalence to the reference drug. This pathway is generally utilized after the reference drug has come off patent (Figure 2 below). A sponsor of a currently marketed unapproved drug would consider this approach if the applicant product was identical to the reference product in active ingredient(s), dosage form, strength, route of administration, and conditions of use.

- 505(b)(2): This application is intended to be used when the sponsor compound is not identical to a reference drug, but does rely on the literature or past FDA findings of safety and efficacy for which the sponsor does not have the right of reference. The degree to which the application relies on information not generated by the sponsor, and the FDA's willingness to accept this information, are critical factors that may reduce the cost of approval for currently marketed unapproved drugs (Figure 3 below).

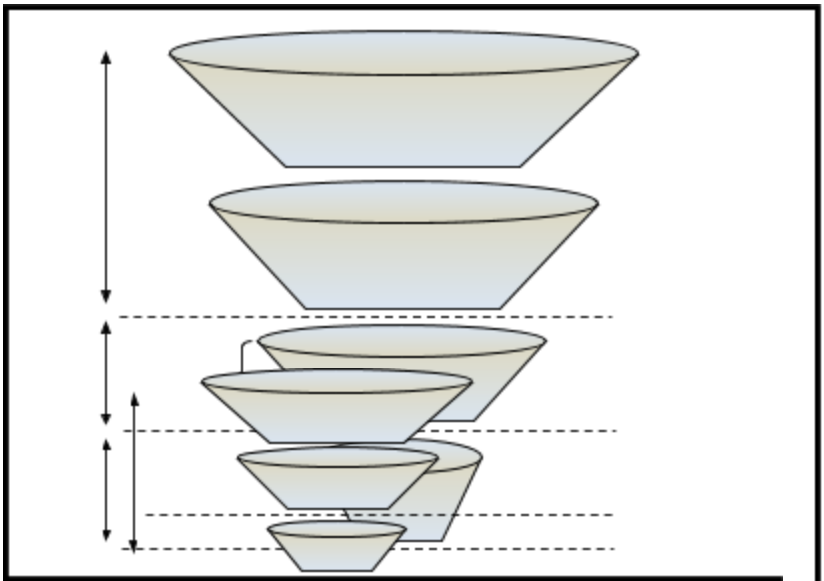

Fig. 1. The 505(b)(1) (***traditional pathway)*** offers high risk with unknown return on investment. *Development may take more than a decade with costs exceeding 100 million dollars.*

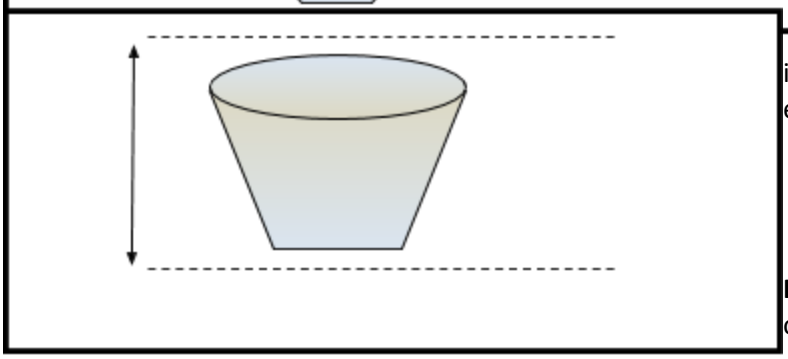

Fig. 2. The 505(j)/Abbreviated New Drug Application (ANDA) (***generic pathway)*** offers a low risk option with known return on investment, but limited to no exclusivity.

Fig. 3. The ***505(b)(2) Pathway*** **(*Hybrid)*** offers a low risk option while

maximizing your return on investment, including 3-5 years market exclusivity.

The objective of the NDA is the same, regardless of which pathway is chosen. However, risks, costs and time to approval can be drastically different. The key is to choose the applicable pathway that poses the least risks, time and expense with the greatest probability for success. For many unapproved drugs on the market, the 505(b)(2) pathway is the best option; however, in order to maximize the benefits of this pathway, sponsors will need to choose their strategic partners wisely.

505(b)(2) Pathway

The 505(b)(2) pathway is an NDA that allows sponsors to provide evidence for the safety and efficacy of a drug for the indications on the product label based on what is already known about the drug in the public domain and/or on file with the FDA. This is typically accomplished through the following:

- Preclinical and clinical evidence of safety and efficacy in the published literature
- FDA findings for safety and effectiveness for a drug approved under a full NDA, known as a reference listed drug (RLD)

According to the FDA's 1999 Draft Guidance on 505(b)(2) applications, the 505(b)(2) can provide a relatively fast-track approval for a wide range of products in the case of new indications, changes in dosage form, strength, formulation, dosing regimen, route of administration, new combination products and new active ingredients. If products meet the 505(b)(2) criteria, this pathway eliminates the need for unnecessary and costly preclinical and clinical studies. Sponsors are able to submit and gain approval in less time than a traditional NDA at less cost, while still enjoying the benefits of exclusivity and compliance (4).

Conceptual differences between a 505(b)(2), ANDA, and 505(b)(1) are illustrated below (Figure 4). In a 505(b)(1) application, findings of safety and efficacy from applicant sponsored studies comprise the foundation of the application (shown in blue). If the application holder wishes to expand on this foundation (e.g by adding a new indication, strength, or route of administration), they may do so through a supplemental NDA (sNDA). In this case, the sNDA is like a roof supported by the original NDA, but expanding beyond it. This option is only available to the sponsor of the original application. For sponsors seeking to file for a currently marketed unapproved drug, the foundational findings of safety and efficacy are the same. However, these findings would be referenced through bioavailability studies rather than a full clinical development program. To support further changes in indication, formulation, or other factors, the sponsor would normally need to conduct additional studies, or reference appropriate literature. This is a key decision point, because most currently marketed unapproved drugs are like the "roofs" illustrated below: they expand beyond the established foundation established by the approved active ingredient and require additional evidence. Determining how to provide that evidence in a manner that produces the least burden is a major component of a 505(b)(2) strategy.

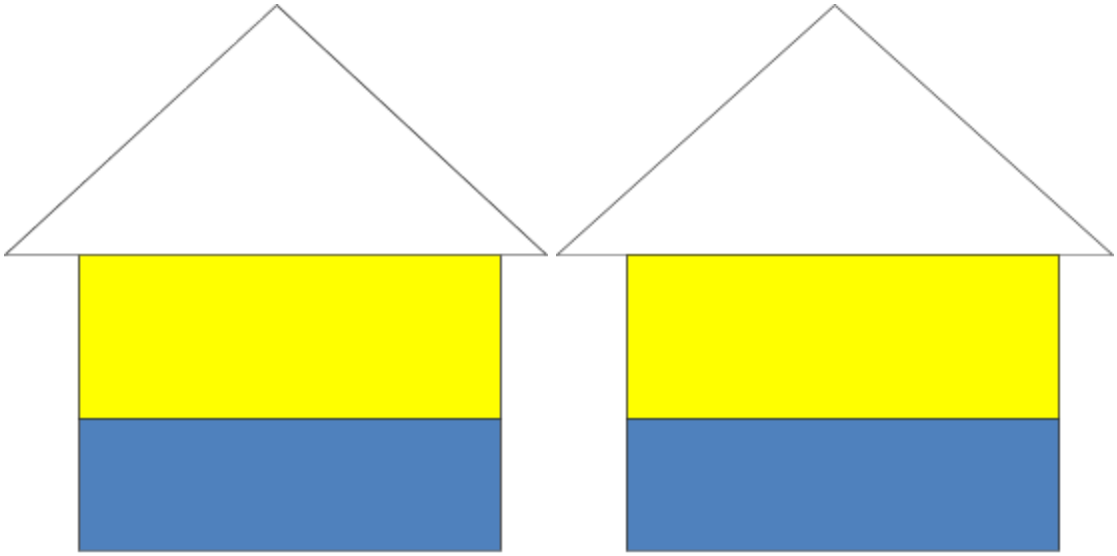

Fig. 4. The 505(b)(2) pathway allows a sponsor to establish a foundation of data from the public domain to gain approval versus conducting costly studies on a drug where safety and efficacy are known.

Challenges with 505(b)(2) applications

A faster and less expensive pathway to approval is ideal; however, as with any NDA application, there are challenges. For example, the FDA's 1999 Draft Guidance on 505(b)(2) applications is largely directed at drugs that may rely on an RLD for safety and efficacy data if equivalence is demonstrated. The guidance does not speak directly to unapproved drug-specific issues, for example:

- Using the literature to prove safety and efficacy when there is no RLD on record with FDA
- Using the literature to find well controlled Phase 3 studies containing adequate details about the protocol, statistical analysis plan and data

It's critical for the success of the application that the 505(b)(2) application present the FDA with all of the safety and efficacy in a traditional NDA. Therefore, it is vital that sponsors align themselves with knowledgeable strategic partners that can help assess the best NDA pathway and successfully navigate the process in the most efficient manner.

Strategic Partnering for a successful 505(b)(2) application

All NDAs are not created equal. The CTD and required evidence for approval remains the same but in the case of the 505(b)(2), process and experience are key. A strategic partner can assist in preparing a detailed plan for how to approach this approval that starts with determining if a drug qualifies for the 505(b)(2) pathway. If the unapproved drug has a RLD, then a demonstration of bioequivalence may suffice for some elements of the label. Additional indications beyond those already on the label of the RLD, or if a RLD does not exist, will require a thorough review of the literature. An effective process meticulously takes into account the following components:

- NDA composition

- Gap assessment
- Selection of search terms
- Database selection for your literature
- Target Product Profile
- Need for Agency meetings
- Identification and processing of applicable literature
- Data summarization and presentation

A comprehensive literature review will be a significant component of a 505(b)(2) application regardless of the need for additional studies. This will be driven by the gap assessment and target product profile. For these 505(b)(2) submissions, the process is essential. You will need to identify a CRO with a strength in their systems and processes to support 505(b)(2) work with a highly experienced team familiar with the particular challenges of literature based submissions.

References:
1. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). *Marketed Unapproved Drugs: Marketed New Drugs without approved NDAs and ANDAs,* Compliance Policy Guide Sec. 440.100. September 19, 2011.
2. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). *Enforcement Actions by Drug Class.* November 28, 2012. Web April 16, 2013.
3. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). *New Drug Application (NDA).* February 21, 2013. Web April 16, 2013.
4. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). *Guidance for Industry: Applications Covered by Section 505(b)(2), (Draft Guidance).* October 1999.

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