AVOIDING RESCUE SITUATIONS

THE GLOBAL 505(B)(2) EXPERTS
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PHARMACEUTICAL SERVICES

ADDRESSING 505(B)(2) PRODUCT DEVELOPMENT CHALLENGES BEFORE THEY BECOME PROBLEMS

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Many 505(b)(2) drug development programs have been derailed or, worse, placed on clinical hold because of incorrect or inadequate advice from consultants inexperienced in 505(b)(2). In this article, we look at three case studies — programs that have been brought to Camargo for "rescue" and provide insight on how to avoid future missteps.

Executing an effective strategy for development of a 505(b)(2) product is challenging for companies that are new to the 505(b)(2) approval pathway. Guidelines for developing products via the 505(b)(2) pathway have been in place in the U.S. for more than a decade,[1] yet many companies that have historically developed new drugs through the new drug application (NDA) pathway (505(b)(1)) or generic medicines through the abbreviated NDA pathway (505(j) ANDA) may not be familiar with the specific processes and requirements of 505(b)(2). Companies and their consultants who rely only on published guidance risk making mistakes in the process that can cost significant time and money, and even derail a project altogether.

Missteps associated with 505(b)(2) filings and processes are often due to misjudgment of the differences that exist in timing and information requirements between 505(b)(2) and traditional 505(b)(1) or 505(j) ANDA proposals. For example, the development cycle timeline for 505(b)(2) products can be much shorter than that of 505(b)(1) products, so there are aspects of the development plan that need to be determined at the pre-IND (PIND) stage for a 505(b)(2) that are not determined until later for 505(b)(1).

Companies navigating the 505(b)(2) pathway do not plan on conducting the same number of clinical studies required for a 505(b)(1) submission and instead leverage existing information and public data to address some of the nonclinical and clinical study requirements. This is one of the most attractive characteristics of 505(b)(2). However, it is still necessary to meet the full safety and efficacy requirements of an NDA. Also, while many of the laws, regulations and guidances for 505(b)(2) proposals are published, many aspects of communication with the FDA are evolving, and the publication of these types of changes occurs more slowly **(see figure 1**). These nuances are often only communicated during FDA meetings. Mistakes due to inexperience or lack of knowledge of current processes can result in the conduct of unnecessary trials, the imposition of clinical holds by regulatory bodies or discontinuation of development due to unnecessary cost concerns.

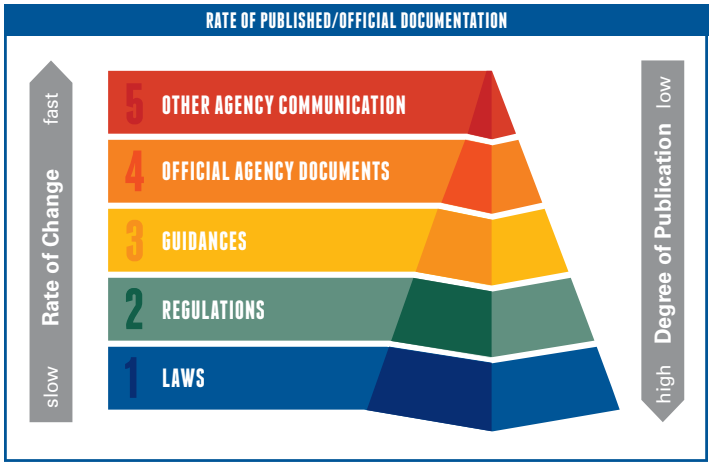


Figure 1

Camargo has worked with a number of clients who have initiated 505(b)(2) projects on their own — and with consultants who were new to 505(b)(2) — and have run into missteps. In the following, we discuss

three examples of situations we have encountered in order to highlight what can happen and how to put misaligned projects back on track. Some details inconsequential to the stories have been changed to protect proprietary information.

CASE 1: INADEQUATE USE OF PUBLIC INFORMATION LEADS TO COSTLY STUDY REQUIREMENTS

In our first case, Company A had initiated product development discussions with the FDA through a regulatory consultant that used existing 505(b)(1) guidance for discussions. The result of its first PIND meeting was a recommendation from the FDA to conduct many clinical trials estimated to cost $25 million and take more than three years. Company A could not afford this and sought Camargo's assistance to rescue the project. Through analysis of the scientific and medical viability of the product, Camargo identified a possible solution. The client had not made sufficient use of data from outside sources — a 505(b)(2) NDA contains full safety and effectiveness reports but allows at least some of the information required for NDA approval, such as safety and efficacy information on the active ingredient, to come from studies not conducted by or for the applicant.

Using proprietary search methods, Camargo researchers were able to identify key publications to support the 505(b)(2) development plan. After arming itself with this new information and following Camargo's recommendations for its approach, Company A conducted another meeting with the FDA. The Agency reversed its decision and agreed that all that was required was a bioequivalence study, which would take mere months and cost less than 10 percent of the studies that were recommended initially.

This highlights the fact that each 505(b)(2) drug approval is distinct, and understanding the nuances of published guidance and unofficial communications is critical to success.

Overall, this approach reduced projected development costs by over $20 million through significantly simplified, timely and compressed clinical trials.

CASE 2: INADEQUATE USE OF PUBLIC INFORMATION LEADS TO CLINICAL HOLDS

A clinical hold can be ordered by the FDA for a variety of reasons, including those related to deficiencies or problems with data related to patient safety, design of the trial and factors in the expected market for the drug.[2] Companies can overcome adverse decisions of this type by ensuring there is a careful analysis of scientific and technical aspects of the FDA decision and subsequent development of remediation strategies to resolve issues.

Company B used a clinically focused consultant company for its PIND meeting, and after progressing to the IND stage, the FDA put the program on clinical hold. There were several reasons for this. First, in the PIND meeting, the information Company B provided was deficient with respect to the nonclinical components. The consultant did not propose that Company B use public information to cover its nonclinical toxicology program. Therefore, the company (and the PIND) did not have toxicology data to support the proposed clinical study. Since neither the client nor the consultant asked questions about this part of the program in the PIND meeting materials, the FDA was silent regarding toxicology requirements. When the company filed an IND and was ready to run the first study, the FDA put the company on clinical hold due to the lack of toxicology data.

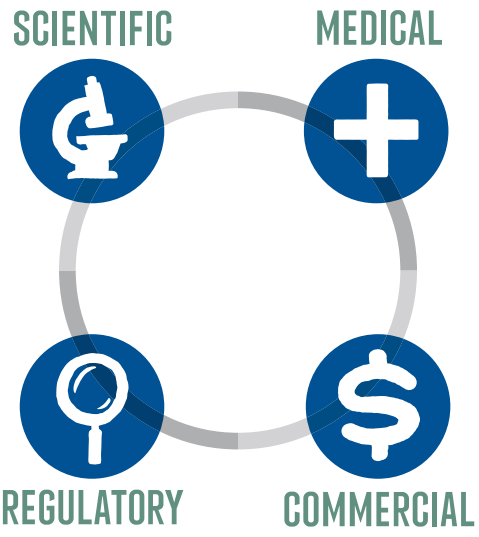
Through application of a thorough feasibility assessment, Camargo's toxicology specialist (a specialty unavailable at the first consulting company) found information in the public domain to cover much of the toxicology requirement. Camargo also determined that the client needed to conduct a small study to cover some additional data to determine whether the product would irritate the stomach lining of patients, as there was nothing in the public domain on this aspect. In this case, Camargo got the clinical hold removed by rapidly identifying and addressing the gaps in the toxicological data.

CASE 3: CHOOSING THE WRONG INDICATION AND FDA REVIEW DIVISION MEANS FAILED PIND MEETINGS

Company C, a specialty pharmaceutical company, had developed a drug that it was interested in getting

approved through the 505(b)(2) pathway with help from a well-established regulatory consultant with significant 505(b)(1) experience. Unfortunately, the consultant relied on published guidance and did not understand how to present a 505(b)(2) product to the FDA, or the requirements of the different FDA divisions. Above all, the consultant did not realize the FDA would categorize the product as a drug-device combination rather than a drug. As a result, the PIND meeting was unsuccessful because the focus of the agenda, questions and materials for the meeting were all wrong. Missteps of this type cost time — it can take up to 60 days to schedule the meeting with FDA — and money due to the effort in preparing for a meeting that does not move the product forward. Most importantly, a failed meeting can derail the whole process because, in general, the FDA only grants one PIND meeting per proposed application.[3]

When the company approached Camargo about rescuing the project, the first step toward rectification was to work through a feasibility assessment. This process involves applying a disciplined approach to evaluate the drug relative to the four pillars of product viability: scientific, regulatory, medical and commercial. The analysis revealed that, in addition to the incorrect categorization of the drug-device, the company's commercial strategy was focused on the wrong market.



The product was developed to treat a solid organ cancer, and the proposed strategy targeted oncology surgeons since the current treatment was excision of the organ. However, Camargo's analysis revealed that the ultimate users of the product would not be surgeons as the drug is able to resolve the cancer while preserving the organ and the drug delivery mechanism does not require surgery. This changed the company's entire approach for compiling support information for submission, market understanding and its sales force. With Camargo's help, the company was able to make the case to the FDA that there was sufficient patient need in this area to warrant a second PIND meeting — a rare occurrence at the FDA. After an excellent second PIND meeting, the product is currently on track. Camargo will also chaperone Company C's product through the European Medicines Agency (EMA) hybrid procedure, which covers products similar to those governed by the 505(b)(2) pathway in the U.S.

COMMON THEMES IN FDA MISHAPS

The three cases above highlight different ways companies can run into trouble when developing 505(b)(2) product development plans. However, there are common lessons that can be learned from and applied to any 505(b)(2) project.

Consultants engaged to assist with the approval process are often clinically focused. This is a relatively common error that product developers can make because they assume the largest expense is going to be the clinical study, and so they believe this is the area of expertise that is most important to engage. These consultants are certainly experts on conducting clinical studies, but are they experts in avoiding or minimizing the need for clinical studies in the first place? The old adage that "If all you have is a hammer, then everything looks like a nail" certainly comes into play. The best clinical trial for your bottom line is one that you do not have to conduct. For 505(b)(2) development, careful analysis, research and planning can significantly reduce the need for clinical trials. However, supporting data from published literature must be assembled and presented to the FDA according to accepted processes, and at the appropriate time.

Consultants with 505(b)(1) or 505(j) experience rely on past experience for 505(b)(2) projects. Consultants often provide regulatory guidance to clients that essentially follows the 505(b)(1) or generics pathway for a 505(b)(2) drug, and, as demonstrated above, this can create problems in a couple of areas. Approaching the 505(b)(2)

drug development process either from a generics perspective that focuses on bioequivalence, or from a 505(b)(1) perspective, can lead to problems with timing and data and can result in missed opportunities, clinical holds and even costly, redundant work.

Consultants don't have expertise in all aspects of 505(b)(2) product development. Most consultants are focused only on regulatory aspects of product development. However, with a 505(b)(2) application, knowing how to execute through the entire development program — from PIND, through formulation, nonclinical, clinical and submission — is essential. Expertise, proven methodologies and sound interaction with the FDA should guide a 505(b)(2) product through the entire approval process. Meetings with the regulatory agencies can be adversarial or they can be outstanding opportunities to reduce risk in the drug development process and gain clarity on the drug development plan — it all depends on your approach.

About the author

Dr. Ruth Stevens has more than 20 years of experience in the development of new drugs and therapeutic agents. She has led more than 100 FDA regulatory meetings in her career and continues to lead numerous meetings. She has authored more than 70 abstracts/publications and is frequently requested as a speaker both nationally and internationally. In addition, Stevens served as an Advisory Committee Member (non-voting) to the FDA's Blood Products Advisory Committee Meeting in 2013.

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