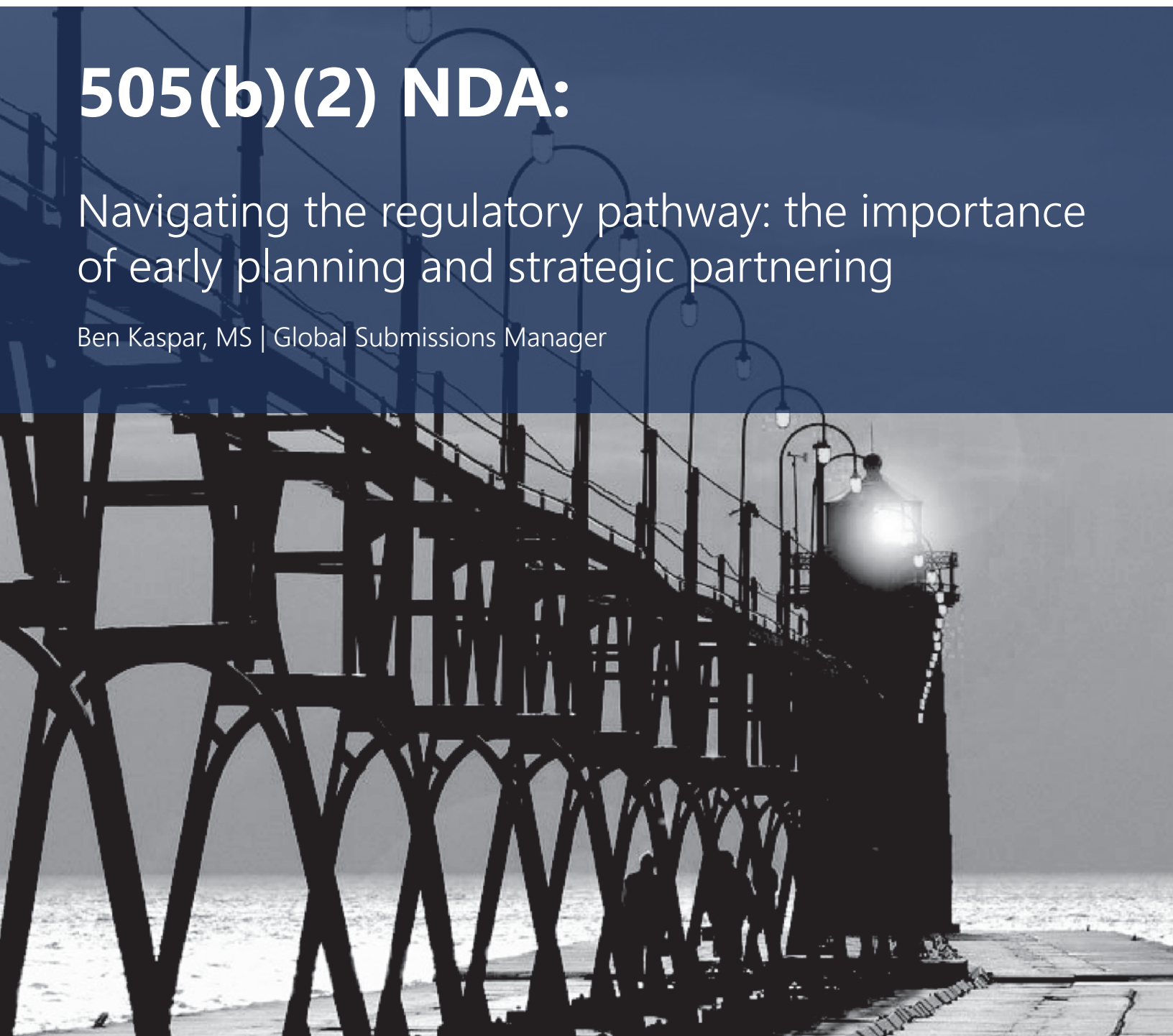


# 505(b)(2) NDA:

Navigating the regulatory pathway: the importance of early planning and strategic partnering

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**T**he 505(b)(2) is a New Drug Application (NDA) containing full reports of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference for use. This is in contrast to the stand-alone 505(b)(1) ANDA application, in which all safety and efficacy data required comes from sponsor-conducted studies, as well as the ANDA (generic) application where this data comes entirely from reference to an already approved formulation. By design, the 505(b)(2) encompasses wide variety of submission scenarios, ranging from moieties that could almost be approved as generics up to those supported by multiple sponsor-conducted Phase 3 studies. Sponsors can refer to the FDA's detailed guidance to determine if their candidate product falls under a 505(b)(2) scenario.



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The 505(b)(2) pathway is a subject of intense interest to sponsors seeking rapid and cost effective pathways for drug approval. It can reduce risks relative to the 505(b)(1) while conferring a degree of market exclusivity commensurate with clinical development effort (3, 5, or 7 years dependent on conduct of a Phase 2/3 study, new chemical entity status, and

orphan status, respectively). The concept of commensurate effort and benefit is important as the process offers expediciencies, market exclusivity, and challenges in equal measure. Because the amount of data presented within a 505(b)(2) can range anywhere between that of a ANDA and a 505(b)(1), development and planning can be unpredictable and intimidating.

This white paper reviews the unique challenges of the application type and describes tools sponsors can use to put their best foot forward during the early stages of 505(b)(2) planning and throughout development. Individually, these tools are simple, and none are unique to the 505(b)(2). Used proactively and in combination, they become powerful time savers.

## **Regulatory History and the Challenge of 505(b)(2) Application Structure**

A historically informed approach to the 505(b)(2) builds an appreciation for structural challenges inherent in the application type. Sponsors of currently marketed unapproved drugs may also wish to review the appendix in the FDA Marketed Unapproved Drugs Compliance Policy Guide for additional historical context.

The application pathway came into existence in 1984 as part of the Drug Price Competition and Patent Term Restoration Act, also known as the Hatch-Waxman Act. This act replaced a cumbersome literature-based application process for generics with a legal structure for approval centered on the relationship between the applicant formulation and a previously approved Reference Listed Drug (RLD). Hatch Waxman supports this structure with a clinical methodology relating applicant formulations and RLDs: bioequivalence studies in the case of ANDAs and relative bioavailability in the case of the 505(b)(2). These concepts form a kind of regulatory Occam's razor ensuring a simple and consistent means of relating the labeling claims of generics and 505(b)(2) compounds with RLDs.

The existence of a simple means to relate reference formulations and unapproved drugs does not always result in a simple application. In fact, the complexity of the 505(b)(2) can rival standalone 505(b)(1) NDAs in a couple of key areas: application structure and supportive data for label claims. To illustrate this, consider the applications for three different products, a reference drug approved through the 505(b)(1) application pathway, an ANDA product, and a 505(b)(2) product (Table 1). In the case of the 505(b)(1) and ANDA, the relationship between label claims and supportive data is generally well defined by, and within, the application structure. This is most obvious in the case of the ANDA, where a single bioequivalence study typically results in a label identical to the RLD; it is also generally true of the 505(b)(1) where the organization of the submission relates label claims directly to adequate and well controlled Phase 3 studies.

In contrast, the 505(b)(2) presents a variable scenario where label claims may be derived from the RLD, new studies, or even literature. As discussed below, the ongoing task of directly and specifically relating these claims to the application is the throughline of 505(b)(2) planning, from the Pre IND stage up to approval.

**Table 1. 505(b)(2) Application Structure and Label Claims**

	505(b)(1)	505(b)(2)	ANDA
Application Structure	Standard "Full NDA" centered on sponsor-conducted pivotal safety/efficacy studies	Variable may be predominantly based on relative bioavailability to RLD, new safety / efficacy Studies, literature, or some combination thereof.	ANDA format centered on bioequivalence and CMC
Label Claims	Based on the results of submitted pivotal safety /efficacy studies	Variable combination of RLD claims, new safety/efficacy studies and literature reports	RLD Label

## The Importance Early Stage Planning

The unique aspects of 505(b)(2) submission structure and label claims are perhaps best illustrated at the pre-IND planning stage. Whereas for a new chemical entity, pre-IND discussion is generally focused on determination of a safe starting dose in humans, the 505(b)(2) discussion will be focused around unsupported label claims and getting FDA agreement on the plan to address them in clinical development. This dramatic difference in early objectives can feel vertiginous to teams unfamiliar with the process, and it is critical that team members understand the expectations and commitment required to successfully navigate the Pre IND discussion. For a 505(b)(2), a lack of clarity after pre-IND discussions can have the same effect as lack of clarity following an end-of-phase 2 meeting for a 505(b)(1) product—they put the program at risk for serious delays.

There are a couple of tools that are useful in getting the most out of the Pre-IND planning process: the target product profile (TPP), and gap analysis. The TPP is a format that systematically associates labeling concepts and supportive data. Sponsors should familiarize themselves with the FDA draft guidance which details the concept and its uses. The particular utility of the TPP in 505(b)(2) planning lies in identifying the existence of any gaps between the proposed study drug labeling, the labeling of the proposed RLD, and any additional sources of safety and efficacy data. Done correctly, TPP construction and gap analysis are essentially a single exercise—a completed TPP should reveal the gaps.

To make the TPP as complete as possible, sponsors should consider the following:

- What is known about the relative bioavailability of the study drug vs the reference drug?
- If there are differences in relative

bioavailability, what is known about the effect of these differences on safety and efficacy?

- If the proposed indication for the study drug is different from the RLD, what is known about efficacy in the indication?
- What new information has become available since the RLD was approved?

These questions should be addressed in the context of a thorough literature search at the time of TPP preparation. In scope, the literature search should cover both clinical and nonclinical research. While reference to the RLD may eliminate the need to conduct non-clinical studies, this should not be taken for granted at the Pre-IND stage.

As the literature search is a significant undertaking, it's important to get the most out of it by consolidating effort across multiple documents including the TPP, Briefing Document, Investigators Brochure, and IND non-clinical summaries. An IND that builds logically on a TPP leads naturally to an NDA that builds logically to an annotated label.

Understanding the FDA's thinking on how relative bioavailability informs the need for additional safety and efficacy studies is also critical at this stage. Sponsors should keep an eye out for FDA publications, such as the recent guidance on Depot Buprenorphine Products, which detail specific PK parameters that may lead to a need for additional safety/efficacy studies. FDA summary review documents on related compounds can be another good source of information. Once the literature search is complete, and the gaps are identified, any uncertainty around the proposed approach to addressing these gaps forms the basis of the Pre-IND questions to the FDA. Buy in on this approach forms the basis of the clinical development plan and sets the sponsor up for long-term success regardless of the complexity of the program.



**Figure 1: Key 505(b)(2) Pre-IND goals**



### Keeping the Tools Sharp During Maintenance Phase

The tools developed during Pre-IND planning stage require continued sharpening during the IND maintenance phase. Ongoing evaluation of literature, RLD labeling, and safety databases are critical in keeping the TPP up-to-date.

Sponsors should also identify any literature considered essential to approval as early as possible. This may not be practical at the Pre-IND stage, but it must be done in advance of the Pre-NDA discussion. The definition of “essential” relates back to the definition of the 505(b)(2): full reports of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant. Sponsors should consult the Clinical Evidence for Effectiveness guidance for more detail on the circumstances under which literature reports may be considered essential. Because the bar is very high, attempts should be made to obtain source records and confirm that any candidate studies were conducted under good clinical practices. Where the FDA deems a published report insufficient to make a regulatory decision, data from that report will be considered supportive only. At the pre-NDA stage, data considered supportive only should not stand alone for any labelling language. The TPP is a good tool to ensure that this is the case.

Following completion of relative bioavailability

studies, safety/efficacy studies, and identification of essential literature, additional gap analyses should be conducted to identify any remaining issues. These issues will form the basis of the Pre-NDA discussion.

### Pre-NDA Planning

Pre-NDA planning and strategy should follow logically from the gap analysis described above. To get specific answers from the FDA, each labelling claim should reference source data within the submission structure with the greatest possible specificity. All of the planning done to this point builds to that objective.

### The Importance of Strategic Partnering

Because the stakes are so high early in development, strategic partnering can be critical to a successful 505(b)(2) project. The benefits of early success carry over throughout development, creating a high dividend for early involvement. At MMS Holdings, we are a data driven CRO and data drives our approach to 505(b)(2) planning. Like the 505(b)(2) application itself, our scenarios for partnering vary depending on the unique challenges of the application but are always fixed on the same goal: a complete application where each label claim is supported by specific data. We don’t specialize 505(b)(1), 505(b)(2), or ANDAs. We specialize in approved NDAs.

## About MMS

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MMS is an award-winning, data-focused CRO that supports the pharmaceutical and biotech industries with a proven, scientific approach to complex trial data and regulatory submission challenges. Strong industry experience and a data-driven approach to drug development make MMS a valuable CRO partner, creating compelling submissions that meet rigorous regulatory standards. With a global footprint across four continents, MMS maintains a 97 percent customer satisfaction rating and was named as the Best Global Biotech CRO in the 2018 International Life Sciences Awards.

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