Your NDA Preparation Should Have Started by Now:
Planning and Managing Your NDA Submission

Throughout our years of preparing and filing Food and Drug Administration (FDA) submissions, Premier Consulting has often encountered sponsors who cannot file a New Drug Application (NDA) or Biologic License Application (BLA) within expected time-frames, most commonly due to a failure to start and complete prerequisite activities before the targeted filing date. In this document, we will highlight those requirements that seem to be the most misunderstood.

CMC Considerations

The timeline for certain chemistry, manufacturing, and controls (CMC) documentation depends on the type of NDA to be submitted. When developing a novel therapy, sponsors can modify certain aspects of their CMC execution as clinical testing progresses. However – particularly in rare disease programs with only one Phase 3 trial, often of short duration – sponsors many times find themselves ready to file clinical data before completing the minimum 12 months of stability testing on the to-be-marketed finished product and API.

On the other hand, an NDA for a drug improvement product utilizing the 505(b)(2) pathway typically has a Phase 1 bridging study, for which the drug product and API generally need to be at the to-be-manufactured stage. In addition, the testing and specifications should be nearly completed prior to initiation of the Phase 1 study and included in the investigational new drug (IND) application.

In addition, working with contract manufacturing organizations (CMOs) can be extremely challenging from a timing standpoint, especially when the inevitable problem occurs. CMOs are subject to current good manufacturing practice regulations, so they have standard operating procedures they must follow. They also have multiple clients, and thus by definition have many demands on their time and resources, particularly their manufacturing equipment and analytical capabilities. Having a quality agreement in place is critical.

For any NDA or BLA submission, it is also essential that the packager and the contract manufacturer for the drug product, the API, and any special excipients be ready for inspections. The FDA may choose to conduct a facilities inspection upon receiving the NDA and reject the filing if the facilities are not ready.

ClinicalTrials.gov

Many first-time NDA sponsors are unaware of the two-fold requirements connected with ClinicalTrials.gov, a website maintained by the National Library of Medicine at the National Institutes of Health. It provides patients, family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions. Depending on the type of trials, an NDA sponsor may be required to register the studies it conducts and the results on ClinicalTrials.gov. Failing to comply with the requirements within the time frames specified in the FDA's regulations can result in stiff penalties, including civil monetary penalty actions.

Document Management

Planning for an NDA or BLA submission begins at the start of development. Sponsors should gather and review required documents throughout the life of a program, while the responsible personnel are still involved – not at the end of development, when contacts are lost and contracts have long expired. Having a secure, version-controlled document system in place from the beginning is essential for achieving a quality and orderly IND, BLA, or NDA submission.

Pre-Filing Requirements

Several activities must be completed before filing an NDA or BLA, and below are the top four areas of difficulty we have encountered among sponsors. Additional requirements depend on the type of drug, indication, review division, and clinical program.

Investigational New Drug Application

An investigational new drug (IND) application is a mandatory filing requirement to permit clinical investigations on drugs not yet approved by the FDA. An IND application allows for the investigational product to be shipped across state lines for use in clinical trials.

Once the IND application has been submitted to the FDA, the review process takes up to 30 days before investigational products may be distributed to investigators.

Pediatric Plan

Whether a drug product is intended for the pediatric population or not, a sponsor's pediatric plan must be submitted and formally approved before an NDA can be filed – unless the product has orphan drug designation. The timing for submission of this initial pediatric study plan depends on a number of factors, and the filing could be required as many as 210 calendar days before the NDA submission.

PDUFA Fee Waiver

The Prescription Drug User Fee Act (PDUFA) fee may be waived for a sponsor's first NDA submission – a potential savings of more than $2 million. However, if the waiver has not been previously approved, the fee must be paid at the time of filing. Since waiver requests have no regulatory priority, many languish in limbo, forcing sponsors to raise additional funds to allow for submission of the NDA.

Proposed Labeling

Many sponsors push back labeling considerations until the last minute, believing that labeling can be produced swiftly. It cannot. Each drug development discipline must work in concert for the proper content, and the art usually requires third-party vendors. Further, NDA applications must include annotated draft labeling, in which the sponsor points to the information in the application that supports the language and content in the draft labeling. As an added wrinkle, the draft labeling must be submitted as a Word document, PDF, and SPL files. The latter stands for "Structured Product Labeling" and requires software that is often too costly for a startup, so a vendor must provide the conversion.

Brand Name

Most drug products have a trademarked brand name used in promotional material, but sponsors often underestimate the time and effort needed to produce that name. While the FDA will accept and even approve an NDA without one, the Agency must approve the brand name before it can be used to promote the product. Generally, sponsors contract a third party to develop candidate names and test them using a protocol similar to the FDA's, a process taking several months.

Financial Certification and Disclosure

An NDA sponsor must certify in the application whether the investigators – or certain of their family members – had a financial interest in any studies they conducted or in the sponsor. This is usually dealt with on an individual basis with a Financial Disclosure Form completed before specific studies begin. However, if there are a number of studies and a large number of study sites, the list of investigators can grow quickly. Those without any interest are dealt with collectively, while those with an interest are dealt with individually. If this information has not been carefully tracked and organized, it can result in a mad scramble when the NDA is being assembled.

Premier Consulting: NDA Regulatory Experts

Given these requirements, not to mention other program-specific considerations, a sponsor should generally begin pre-filing activities at least 12 months in advance of an NDA submission.

Premier Consulting has experience with NDAs across all therapeutic areas and has made submissions to the FDA's Centers for Drug Evaluation and Research, Biologic Evaluation and Research, and Devices and Radiological Health divisions. Our experts can help you determine which actions you need to take to prepare for your submission and when during development you should initiate them. With over 20 years of experience and frequent interactions with the FDA, we have the knowledge and quality assurance capabilities to ensure your NDA or BLA meets every requirement and expectation for approval. Contact us to learn more.