

Relevant Applications For Drug Development and Approval

Researchers who understand the drug approval pathway may travel a smooth road from conception to approval.

BY ARON SHAPIRO

In the previous column we outlined the benefits of early, meaningful interactions with the US Food and Drug Administration (FDA) in an effort to facilitate the drug development process (see July/August issue of *Retina Today*, pages 26–27). This installment describes the next step by dissecting the Investigational New Drug (IND) process, exploring the components of a New Drug Application (NDA), and covering the events between an IND and an NDA submission.

IND APPLICATION

Pre-IND meetings provide sponsors the opportunity to gain direct feedback on their program prior to submitting an IND application. The FDA does not require these meetings, but they help prevent clinical holds, which delay the progress of clinical trials. Whether or not a pre-IND meeting has been held, those seeking to advance their development programs by conducting clinical trials must submit an IND application. Submissions can be completed either on paper or electronically. The primary purpose of the IND submission is to ensure that subjects will not face undue risk or harm, so the central focus of the submission should be on the investigational plan and protocols.¹

The IND application must include FDA Forms 1571, 1572, and 3674; a table of contents; an introductory statement and general investigational plan; investigator brochure; protocols; chemistry, manufacturing, and control information; pharmacology and toxicology study results and findings; previous human experience with the investigational drug (if there has been no previous experience, the submission should state that); and any other additional or relevant information needed for review of the application.² Use serial number 0000 for the initial IND application with FDA Form 1571. This form must accompany every subsequent submission of the IND, and

the serial number should increase by increments of 1 (eg, SN0001, SN0002, etc.) each time. FDA Form 1572 provides investigator information and is specific to the protocol proposed in the IND application. FDA Form 1572 must be submitted for each principal investigator at all additional sites added to the study (if any sites are added). FDA Form 3674 is a commitment that the study will be registered with ClinicalTrials.gov.

The sponsor must wait 30 days before initiating any clinical trials after the IND application is submitted. The FDA will issue an IND acknowledgement letter, which includes the IND number, receipt date, and contact information. During the 30-day waiting period, the reviewing division will determine if the study is reasonably safe to proceed, or if the study will be placed on a clinical hold. A clinical hold can either be full (delay/suspension of all clinical studies under an IND) or partial (delay/suspension of only part of a clinical study under an IND). The FDA commonly issues clinical holds because of a lack of needed safety monitoring in the clinical trial design or because the investigators provided too little information on the drug manufacturing process. Also, the FDA may issue a clinical hold if additional evaluation is required as a result of toxicology trials or if the investigator brochure is misleading or incomplete.

NDA SUBMISSION

Submission of an NDA is the formal step that a sponsor takes to request that the FDA approve its product for sale and marketing in the United States.³ This is a very complex process—applications, designed to tell a product's entire story, must be extremely detailed and may be hundreds of thousands of pages long. An NDA includes all of the data gathered during nonclinical phases in addition to human clinical trials conducted as part of the

TABLE. PRESCRIPTION DRUG USER FEE RATES FOR FISCAL YEAR 2014⁶

An application requiring clinical data	\$2 169 100
An application not requiring clinical data, or a supplement requiring clinical data	\$1 084 550
Establishment fees	\$554 600
Product fees	\$104 060

IND application.³ Additional information on the product's mechanism of action and how it is manufactured should also be included. Once an NDA has been submitted, the FDA has 60 days to decide whether it should be filed and subsequently reviewed.^{3,4}

The official review time is the length of time it takes the FDA to review an NDA and issue an action letter, which is an official statement informing the sponsor of the FDA's decision. The approval time frame includes time for the FDA to review the initial submission of an NDA, in addition to time needed for the sponsor to address any deficiencies identified by the FDA and subsequent FDA review. These deficiencies might include product labeling revisions, new data analysis acquisition, or the need to conduct additional studies. An FDA review team composed of doctors, chemists, statisticians, microbiologists, pharmacologists, and other industry specialists evaluates whether the studies submitted as part of the NDA demonstrate the safety and efficacy of the product for its proposed use. Reviewers will carefully comb through the NDA and examine each study for potential weaknesses in design or analysis. There are 3 possible outcomes for an NDA: approved, meaning that the product can be marketed; approvable, meaning that minor issues must be resolved prior to approval; or non-approval, which indicates that there are significant issues with the application and that substantial additional information is needed.

The Prescription Drug User Fee Act of 1992 authorizes the FDA to collect fees from NDA applicants in exchange for accelerating its review process.⁵ The schedule of fees for fiscal year 2014 can be found in the Table. The FDA's Center for Drug Evaluation and Research operates under the standard that it will review and act on at least 90% of NDAs for standard products no later than 10 months after the applications are received. The Center for Drug Evaluation and Research also reviews priority submissions (applications for a product that provides a significant therapeutic or public health advancement) within 6 months.⁴

WHAT IS IN BETWEEN?

After a sponsor submits an IND, it can begin clinical trials after a 30-day waiting period (unless the FDA has issued a clinical hold). Clinical trials used in drug development are typically described by phase, and generally consist of 3 premarketing clinical development phases,

followed by a discretionary fourth phase intended to provide postmarketing information.

Phase 1

These studies are usually conducted using healthy volunteers, as it is the first time an experimental product is tested in humans. Phase 1 trials usually consist of a small group of approximately 20 to 80 patients and are designed to determine the drug's safety, identify frequent side effects, and explore the drug's metabolism and pharmacokinetic and pharmacodynamic profiles.³

Phase 2

These studies focus on the drug's effectiveness and further determine its safety. Phase 2 studies enroll approximately 100 to 300 patients who have a specific disease or condition.³ Most phase 2 studies are randomized, double-masked, controlled trials. Phase 2 trials frequently include dose-ranging evaluations to determine the most effective dose or concentration and frequency of treatment. Following the completion of phase 2 testing, the FDA and sponsors may meet to discuss what large-scale phase 3 studies might look like.³ Frequent interaction with the FDA facilitates the development process, as these discussions serve to address potential complications before they occur.

Phase 3

If effectiveness is demonstrated in phase 2, a large group of subjects (ranging from several hundred to over 1000) are enrolled in a phase 3 study to confirm the treatment's efficacy. These trials may also continue to test the investigational treatment in different dosages and populations, compare it to commonly used therapies, and evaluate the overall benefit-risk relationship. Phase 3 trials must be completed on the exact formulation of the investigational drug that is to be marketed. Up to this point, variations in formulation and manufacturing are allowed.

Following the completion of phase 3 trials, when all studies designed to support the desired safety and efficacy claims have been completed, sponsors may also meet with the FDA for a pre-NDA meeting.³ Sponsors should use this meeting to ensure that adequate knowledge has been generated to support a successful filing of an NDA. Discussions may center on whether evidence of effectiveness was seen

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in phase 3 trials, the need for risk management, and plans to address potential problem areas. A pre-NDA meeting can also discuss technical goals, such as seeking agreement from the FDA about the format and content of the submission.

Phase 4

Following a successfully filed NDA, or as part of the approval process per FDA request, additional studies may be conducted after the product is marketed. Phase 4 studies, often called postmarketing studies, are used to gather additional information in real-world settings, such as information about the product’s efficacy, the effect of the marketed product on quality of life, and long-term safety and efficacy data. Whether mandated by the FDA or pursued by the sponsor, phase 4 trials are designed to improve researchers’ and clinicians’ understanding of a therapy’s potential uses and its long-term benefits for health and quality of life.

CONCLUSION

The drug development timeline from IND filing to NDA approval is complex and highly variable. Much of it depends on the sponsor’s preparation. As your development program progresses, it is important to keep later milestones in mind so that your program is as comprehensive as possible. Being well versed when it comes to FDA regulations and expectations for the content, submission, and review of INDs and NDAs will help facilitate your drug development program. ■

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