Meeting With FDA Can Increase the Probability of Product Approval

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Formal meetings with reviewers at the US Food and Drug Administration (FDA) are among the most important and useful resources available to sponsors of medicinal products seeking marketing approval in the US. These meetings provide an opportunity for companies to discuss product development strategies with the regulators and clarify interpretations of the regulations. In 1997, under the *Prescription Drug User Fee Act (PDUFA*), the US Congress mandated FDA meetings with applicants to guide and assist them in planning and submitting appropriate information in all the steps leading to marketing a medicinal product.[1] Since then, FDA personnel have participated in hundreds of meetings each year covering all kinds of applications. Although this article uses drug terminology, the information applies to biological products, medical devices, generics, over-the-counter drugs and all other products regulated by FDA.

Why Meet With FDA?

The ultimate goal of any product development project is marketing approval. In the US, a sponsor needs to demonstrate its product's safety, efficacy and consistency using a series of tests and process developments such as animal experiments, clinical trials and optimizing the manufacturing steps in order to gain that approval. Moreover, each product has unique requirements for testing based upon scientific criteria to establish significant benefit over its risks. It is generally agreed that a given product could require up to 10 years and hundreds of millions of dollars in preparation for formal review by FDA. Considering the huge stakes involved and that FDA makes the final decision as to whether the information provided in a given application is sufficient to approve or reject, it makes a lot of sense to discuss the contents with FDA reviewers prior to submission and even prior to testing. A sponsor can get direct feedback from the reviewers about the appropriateness of proposed tests (animal and clinical trials), sufficiency of data and adequacy of the format in which the information is proposed to be presented. Sponsors can learn about agency concerns and hear opinions about all the tasks planned and completed. This input can enable the applicant to avoid pitfalls and troubleshoot issues before formal submission of data, leading to a higher probability of success.

FDA strongly recommends that the sponsor request meetings with its reviewers as many times as needed and as early in the development process as possible. FDA has released a few guidance documents to help sponsors prepare for these meetings[2] and also published an analysis by an independent organization highlighting the importance of presubmission meetings with FDA in achieving an accelerated and favorable response from the agency.[3]

FDA Meetings: Integral to the Review Process

FDA reviews continue throughout a drug product's lifecycle. Before the initiation of the first clinical trials, a sponsor is required to provide the scientific rationale for the product and demonstrate its safety at the first proposed dose for human consumption in an Investigational New Drug (IND) application to FDA. The information submitted in the IND varies based upon product and target indication. The first time a sponsor meets FDA reviewers typically is at a pre-IND meeting to discuss the information included in the proposed application. Thereafter, the sponsor may meet reviewers at various times, as shown in **Figure 1**, to discuss product development progress and subsequent steps.

Aside from the pre-IND meeting, the most important meetings are: discussion of Phase 2 clinical trial data in preparation for the Phase 3 pivotal clinical trials—the End-of-Phase 2 (EOP2) meeting; and the pre-NDA (New Drug Approval) meeting to discuss the data from the studies completed by the sponsor along with the format and content of the proposed application. In addition, sponsors usually request meetings to discuss the interim data from Phase 3 studies and clarify any pending issues during NDA review.

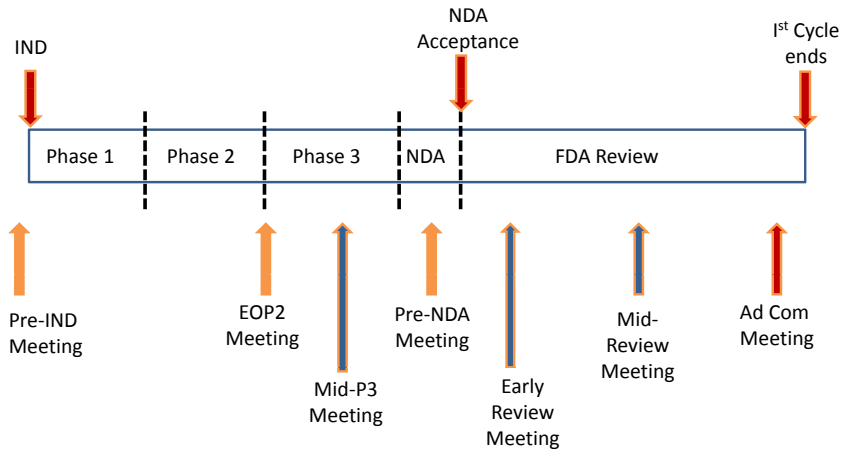
FDA personnel consider meetings with the sponsor an integral part of the review process that typically lead to greater success in getting an approval decision.[3] These meetings provide both parties an opportunity to discuss the findings and their implications for further steps, clarify any confusion about the data, review regulatory requirements for a given product, analyze the scientific rationale and reach an agreement on the subsequent steps in development. Internally, FDA follows a "continuous review" process whereby project development progress is closely and continuously monitored by the reviewing division via review of materials sent by the sponsor, internal meetings and requests for further information from the sponsor, as well as periodic meetings with the sponsor.

Categories of FDA Meetings With Sponsors

Under *PDUFA*, a sponsor has the right to request a meeting with the FDA reviewing division to discuss development steps regarding a proposed medicinal product leading to its marketing approval. However, these meetings are specifically to assist in development of viable products and not for discussions about a product concept or scientific idea. In general, these meetings are approved unless FDA perceives that there is no viable product being proposed.

There are three main kinds of FDA meetings under *PDUFA*:

Figure 1. FDA Review Process



FDA review is an ongoing process: key in-person meetings and their time points are highlighted. Dark arrows represent critical meetings while light arrows indicate additional mid-cycle meetings commonly requested by sponsors. EOP2 = End-of-Phase 2, Ad Com = Advisory Committee.

- Type A meetings—These are urgent or critical meetings primarily to resolve safety and clinical hold issues. Typically, they are convened for quick resolution of issues, such as reports of an adverse event, that could affect the safety of study participants and lead to an interim or permanent halt to an ongoing clinical trial. In addition, Type A meetings can be requested for resolution of disputes between the reviewers and sponsors or for special protocol assessments. Type A meetings must be scheduled within 30 days of the request.
- Type B meetings—Most procedural meetings such as the pre-IND, EOP2 and pre–NDA meetings fall into this category. This is the most common kind of meeting granted by FDA, intended specifically to meet *PDUFA* requirements for assistance with new product development. Type B meetings are typically scheduled within 60 days of the request.
- Type C meetings—These are also called miscellaneous meetings and are used to designate any meeting that does not fall into the above two categories. These meetings could be used to discuss issues related to manufacturing or for data clarification. These are the least common meetings and usually require the sponsor to demonstrate an urgent need that can be satisfied only with an in-person meeting with FDA personnel. These meetings are scheduled within 75 days of the request.

In-person meetings are not the only avenue for discussing issues and getting feedback from the agency. FDA also approves telephone or video conferences, particularly if a key member from the sponsor's team cannot attend in person. A sponsor can also send written requests to the FDA team seeking clarifications, advice and feedback. All communications are documented and become part of FDA's official discussion with the sponsor.

Timing the FDA Meeting Request: Asking the Right Questions at the Right Time

With growing awareness of the importance of direct discussions with FDA, increasing numbers of sponsors submit requests for meetings. To make the most of a meeting, the sponsor needs to get definitive answers from FDA, and this requires assurance that there is enough background information available to effectively discuss and resolve the issues in question. For example, the main goal of a pre-IND meeting is to reach agreement to initiate the first clinical trial. Therefore, specific information regarding this topic must be available before scheduling the meeting. The sponsor must have good-quality product manufactured under Good Manufacturing Practice (GMP); have completed toxicity studies in animals per the latest regulations and calculated the recommended dose; have a good scientific rationale for the indication targeted, mechanism of action and possible adverse reactions; and a have clinical development plan. It is very important for the sponsor to assess whether this information is sufficient for a scientific discussion.

Another important aspect of optimizing meeting value is to prepare specific, relevant questions. FDA typically prefers that the sponsor suggest the development plan, to which

the agency indicates its agreement or concerns instead of directly suggesting what specific tests are needed. Hypothetical questions about future clinical studies or regulatory pathways might elicit general, noncommittal answers that consume limited time needed for specific questions.

Requesting and Preparing for FDA Meetings

Numerous publications and trainings are available to help prepare a formal meeting request and to prepare for the meeting, most important being FDA's guidance about meetings. The first step is usually identifying the appropriate review division at FDA. FDA divisions are mostly categorized according to disease and type of product. Contact information with names of key personnel in each division can be found on the FDA website (www.fda.gov). In case it is not clear what division would be most appropriate, the sponsor can contact the most likely division and request guidance. FDA personnel are usually very helpful in identifying the correct division over the phone. The same division reviews the product during its entire lifecycle so, once confirmed, it should receive all subsequent meeting requests and other material.

The initial meeting request should contain sufficient information, as described above, for FDA to evaluate its merits. In addition, the sponsor should include the specific questions to be discussed, the specific reviewers (e.g., toxicologists, clinical specialists, chemists, etc.) desired to participate and the list of sponsor's own experts who plan to attend. FDA responds within two to four weeks, either granting the meeting or describing in detail why the agency believes a meeting is not necessary. Also included in the FDA response is the potential IND number and direct contact information for the regulatory project manager (RPM) assigned. The RPM is the main contact for all further communications with FDA.

The sponsor is asked to submit updated information at least four weeks before the scheduled meeting. This pre-IND information package should contain detailed information such as complete CMC information to date, detailed preclinical study summaries (full reports are not necessary), complete review of literature, key references, proposed nonclinical program and proposed clinical development program with a synopsis of protocols (full drafts of the first proposed protocol can be submitted but are not necessary).

Figure 2. Different Meeting Types

- Pre-IND meetings
  - Strategic discussion for the entire program
  - Commitments from sponsor and FDA
  - Considered one of the most important by FDA
  - Heavy on regulatory planning and overall CDP aiming to initiate first clinical study
  - Triples the chance of IND approval without delay
- End-of-Phase 2 and pre-NDA meetings
  - Discussion of results and impact on application
  - Doubles the chance of first-cycle approval
- Mid-cycle meetings
  - Very specific discussions
  - Granted less commonly but response is still provided

About a week prior to the sponsor meeting, FDA convenes an internal meeting to review the pre-IND information package and make preliminary comments, which are forwarded to the sponsor to help prepare for the meeting. These comments encompass FDA's initial responses to the sponsor's specific questions based upon the information provided and current understanding of the scientific rationale. It is advisable for the sponsor to review the preliminary comments carefully and prepare follow-up responses and discussion points based on them for the meeting.

The sponsor should prepare adequately for the meeting. Different kinds of meetings need different kinds of preparation (see **Figure 2**). Typically, meetings are set for one hour and no time extension is given. Therefore it is necessary for the sponsor to utilize the allotted time appropriately to obtain the best outcome. While the sponsor's preparation should begin when the meeting request is submitted, final reviews and training should take place after receiving FDA's preliminary comments. Preparation includes two major components: establishing scientific rationale for the project and maintaining good communication channels. Mock discussions delineating expectations and compromises, establishing a team leader, assigning roles to all sponsor attendees and timing discussions are all good tools for practice.

Based upon the preliminary response from FDA, the sponsor may make changes to its attendees. These usually include decision makers (CEO, CSO, etc.), subject matter experts (toxicologists, CMC head), medical specialists (physician consultants) and regulatory specialists. Ideally, the sponsor attendees should match the FDA experts to allow detailed scientific discussions.

Logistics of the FDA Meeting

As mentioned above, the meeting is usually 60 minutes but may be longer if multiple divisions participate, for example a biological product for treating cancer may involve experts from both CBER and CDER. The FDA team consists of all the experts specifically requested by the sponsor and possibly additional personnel. The discussions are led by the FDA review team leader, while other experts who reviewed individual components of the information package are also available to discuss them, as needed. The FDA division director or designee is also present. The RPM manages the meeting and is responsible for documenting official minutes.

The key objective of the meeting is for the sponsor and the FDA review team to discuss the scientific and regulatory issues related to the product. Sponsors are encouraged to openly discuss all their plans and the FDA team presents any major concerns. The discussions are usually conducted in a very collegial and non-confrontational manner, where the scientists on the two sides discuss the issues and come to agreement on potential resolutions. The discussion centers on the specific questions submitted by the sponsor in the meeting request. Additional questions are permitted but FDA usually defers any major additional questions to a later meeting upon review of the relevant additional information.

It is recommended that the sponsor submits its notes from the meeting to the RPM within a few days of the meeting so they can be considered for inclusion in the official minutes. FDA issues the official minutes of the meeting in about 30 days, summarizing the key discussions and action items. Corrections, follow-up comments and further clarifications can be communicated to the RPM at any time after the release of the official meeting minutes.

Periodic FDA Meetings Increase Chances of NDA Approval

An independent survey and analysis of the relationship between the number of FDA/sponsor meetings and the probability of NDA approval was conducted by Booz Allen Hamilton for the period 2002–07.[3] The analysis concluded that good communication between FDA and sponsors, established via periodic meetings and other methods, leads to a higher rate of first-cycle approval. Sponsors of successful applications had an average of 25 interactions with the agency. Another important factor was

the sponsor's responsiveness to FDA's concerns. Not surprisingly, successful applicants actively followed up on recommendations. It was also found that most unsuccessful applications failed for one deficiency. Most of these issues, according to the survey, could have been resolved relatively easily with sponsor-FDA communication before the submission of the application. Another interesting finding was that most of those unresolved deficiencies over which unsuccessful applications failed remained so because the sponsor had not asked the most relevant questions in the opinion of the FDA personnel interviewed.

Conclusion

Available to all sponsors, FDA meetings are unquestionably an invaluable tool to increase the chances of application approval. Proactive discussions with FDA throughout all the development steps can make a crucial difference in success or failure. FDA reviewers are involved in many similar applications and hence have unique insight into potential issues with any given product. Although FDA cannot discuss confidential information about competing or related products, sponsors do get the benefit of the agency's experience regarding potential pitfalls. Successful interactions with FDA depend upon thinking scientifically, posing appropriate questions and paying close attention to concerns highlighted by the regulators. Requesting and optimizing these meetings can lead to better products faster.

Reference

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