

Managing primary IND applications with the FDA

Author

Heimo Scheer, Vice-President, Regulatory Affairs, Celerion

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Abstract

For those who have taken the decision to conduct clinical studies in the United States, there is one major challenge: how do you deal with the regulatory process in order to obtain approval for your study as quickly and as efficiently as possible? The aim of this article is to provide you with considerations for the pre-filing phase, the authoring and publishing of the investigational new drug application (INDA) phase, and the submission and review phase, so that you may be able to succeed in your goal speedily and effectively.

The pre-filing phase

While scientific investigations in support of the test drug will probably pre-date the filing of the IND by many years, direct planning activities for the filing of an IND should commence approximately 12 months before the actual filing date. During this period, it is understood that investigations expected to provide pivotal data and information for the IND are still underway (eg, stability data for the drug substance; safety data as provided under ICHS7A – ‘Safety Pharmacology Studies for Human Pharmaceuticals’).

The first key activity is the collection of all reports which will need to be filed with the IND. In contrast to submissions outside the US, the FDA requires that all reports intended to support the IND be submitted as an integral part of the submission. There is no hard rule as to what studies need to be submitted, but your perspective should be at least two-fold: first, any claim or statement provided in the investigator brochure should be complemented in the submission by the underlying report, and second, any report presenting data relating to any possible safety issue should be covered in a report.

Information in the public domain is acceptable to the FDA depending on the intended use of the information: an article that addresses the general pharmacology of the drug is only supportive evidence for the IND; safety data on the other hand would be viewed as pivotal data where the FDA expectation is that the sponsor of the IND will have direct access to the underlying raw data, a requirement generally difficult to meet with public information.

During the compilation of the data, it is natural to encounter results which stimulate the reader to wonder how the FDA would interpret the results and what their ensuing actions might be. In order to remove unpleasant yet preventable surprises after the filing of the IND, the FDA encourages, but does not require, pre-IND meetings where key matters can be discussed.

The FDA provides a useful guidance describing the mechanism of meeting request, agency timelines, and a general Table of Contents for the Debriefing Package.¹ Per the guidance, only one such meeting is granted by the FDA; therefore, the timing of the meeting and nature of the questions asked are critical. If the questions are asked too early in the development process, then it will be problematical to ask what subsequently turn out to be more significant questions; if the questions are asked too late and the FDA requires additional work be done, then there could be a delay to the filing of the IND with ensuing delays in trial start-up and possible corporate repercussions. Experience suggests planning a pre-IND meeting four to six months before the planned IND filing date provides a reasonable balance between the risks of asking too early and asking too late.

A drug which has not been approved previously by the FDA will be evaluated with any one of the approximately 15 divisions in the Office of New Drugs. While not always obvious, a little perseverance, homework, and the names of the reviewing divisions will allow you to determine the appropriate reviewing division (eg, an Alzheimer’s drug will be reviewed by the Division of Neurology Products; a novel anti-glaucoma drug will likely be reviewed by the Division of Anti-Infective and Ophthalmology Products; an eczema drug by the Division of Dermatology and Dental Products). The appropriate reviewing division should be confirmed by contacting the FDA before any documents are actually shipped. Most clinical studies in support of a generic drug application do not need to be supported by an open IND, as US regulations provide an IND for these types of clinical studies. However if an IND is required, questions should be brought to the Office of Generic Drugs.

One approach to finding who to contact is to find the Approval Letters for previous approved drugs under Drugs@FDA,² determine which division signed off on the letter, and then contact a project manager in that division via a searchable listing of relevant phone numbers.³ Do not expect to succeed with one call or one email, but perseverance will eventually bear fruit.

Questions should be formulated with the general approach of trying to get the agency to either agree or disagree with any position you are taking. IND review questions should be avoided. For example, a question asking whether the agency will accept chemistry information even if stability information is not complete will probably generate a useful response (eg, a proposal of submitting one month accelerated data only with a commitment to file additional stability data at a later date); a question asking whether a specific set of stability results are acceptable would most likely be viewed as a

Table 1: Mapping of traditional IND, IND in CTD format, and CTA (EU)

Traditional IND (Title)	IND in CTD format* Module No (Title)	CTA (EU)
Item 1 (Form 1FDA-1571)	1.1 (Application Forms)	EudraCT Application Form
Item 2 (Table of Contents)	1.1 (Table of Contents)	Section J
Item 3 (Introduction)	2.5 (Clinical Overview)	n/a
Item 4 (General Investigational Plan)	1.13.9 (General Investigational Plan)	n/a
Item 5 (Investigator's Brochure)	1.14.4.1 (Investigator's Brochure)	Investigator's Brochure
Item 6 (Protocol)	5.3 (Specific Study)	Protocol
Item 7 (Chemistry, Manufacturing, and Control Information)	3.2.S; 3.2.P (Quality)	Investigational Medicinal Product Dossier
Item 8 (Pharmacology and Toxicology Information)	2.4, 2.6 (Nonclinical Overview; Nonclinical Written and Tabular Summaries)	n/a
Item 9 (Previous Human Experience)	2.5, 2.7 (Clinical Overview; Clinical Summary)	Active Trials

*<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163175.pdf>

reviewing question for which you will not be provided an answer in a pre-IND meeting.

Pre-IND meetings can be held either as face-to-face meetings or by teleconference. Disappointment should not reign if only a teleconference is granted or if no meeting is granted at all. A good debriefing package will often result in a written response from the FDA answering all questions satisfactorily, thereby obviating the need for a meeting. A teleconference is easier to schedule, manage, less costly, and generally just as effective as face-to-face meeting. A distinct advantage of a teleconference over a face-to-face meeting is provided by the option that the FDA reviewing team or the sponsor can mute the phone, come to an internal consensus, and then provide immediate feedback on the question. Do not be surprised if the FDA team are on mute for 10-15 minutes before they respond. The only message to be read into a longer mute is that the FDA is taking the necessary time to arrive at a consensus which they can convey immediately over the phone.

Official meeting minutes will be provided by the FDA as soon as possible after the meeting (generally within 5-8 working days). Nevertheless, submission of the sponsor's version of the minutes will be accepted by the FDA and, if supplied within a day or two of the meeting, should help to avoid any misunderstandings.

The principal aim of the pre-IND meeting is to avoid any judgements by the FDA which would preclude the conduct of the clinical trial, or might result in a clinical hold on review of the IND. By

familiarising the FDA with your drug and your intended clinical plans, you are trying to ensure a clear path to the clearance of your IND with as few surprises as possible.

IND format

The format of an IND can take multiple shapes: from a submission in eCTD format to a paper submission in traditional format or a mixture thereof can be acceptable. The granularity of traditional format is guided by 21CFR312.23(a)-(f)⁴ and consists of eight principal sections (termed "Items" 1-8) which need to be authored for IND. Item 1 (Cover letter; FDA Form 1571), Item 2 (Table of Contents), Item 3 (Introductory Statement), and Item 4 (General Investigational Plan), are unique to an IND. Item 5 (Investigator's Brochure), Item 6 (Protocol), Item 7 (Chemistry, Manufacturing, and Control [CMC] Information) and Item 8 (Pharmacology and Toxicology Information) can be reused in other regulatory submissions if appropriately structured. A common hybrid IND submission type presents Item 7 in CTD granularity under 3.2.S for Drug Substance and 3.2.P for Drug Product.

In addition to providing the FDA reviewer with a document which is easy to navigate, the advantage to the sponsor is forward-looking: Item 7 in CTD format can easily be updated and maintained in a format which is in essence "NDA-ready". If the traditional format of providing CMC information in a narrative as deemed appropriate by the sponsor at the time of initial IND filing is followed, then incorporation of the multiple CMC updates to Item 7 over the years may prove particularly

challenging at NDA time. Individual CMC reports need not be provided for the reviewer as long as key raw data are provided within Item 7 (eg, HPLC tracings showing impurities). While Item 8 can also be prepared in CTD granularity as provided under Module 2.6 'Content of Nonclinical Written and Tabulated Summaries', the paucity of the information available at this time can render Item 8 more difficult for the reviewer to navigate and understand than the traditional format. A high-level mapping of a traditional IND to a CTD-formatted IND as well as Clinical Trial Application (CTA) in the EU is provided in Table 1.

Whichever format is chosen to present the data and information, consideration should be given to present the data in the most concise form for ease of review. As an IND comes with the supporting reports, reviewers seeking details will go to the reports and render their own conclusion.

From a publication perspective, three copies of the primary IND application are submitted in off-size, special FDA folders coloured red (archival), green, and orange. These folders can be ordered from a number of specialty suppliers. All volumes should be appropriately tabbed to ensure smooth and easy navigation by all reviewers.

If the sponsor chooses to submit the IND electronically in eCTD format but has never done so before, then submitting a sample IND to the FDA is highly recommended. The eIND will not be reviewed for content; rather the IND will be reviewed from a technical perspective only to ensure that the submission meets FDA electronic specifications and requirements.⁵ All documents should be provided with a referenced xml backbone, in a readable pdf format, bookmarked, and appropriately hyperlinked. Failure to submit your eIND without adherence to these electronic requirements could result in significant delays to the IND review.

Submission process

Whether a pre-IND meeting has been held or not, an email or phone call to the FDA project manager about one month prior to submission data is strongly advised. The FDA does not have a group dedicated to reviewing clinical trial applications; essentially the same staff who review NDAs and post-approval supplements are charged with reviewing INDs. As a consequence, the project manager has to coordinate and prioritise multiple reviews among the various clinical pharmacology, toxicology, medical, chemistry, and possibly statistics reviewers with the Division Director signing off on the approval. Simply submitting your IND should not impede the agency's statutory requirement of a 30-day review, but a surprise submission will not help with building your relationship with the project manager. As INDs require continual updating and management even if the research activity is outside the US, with the filing of an IND you have entered into a long-term relationship that will include at least some of the same personnel up to and, with any luck, beyond the approved NDA for your drug.

Review process

Once the required three copies of the IND have been submitted, expect a call or an email from the project manager for additional copies. The project manager may ask for one additional copy or for twenty additional copies. Hopefully the reviewer will limit additional desk copies without the supporting study reports, but abiding by FDA requests for additional copies is highly advised. An official acknowledgement letter with the assigned IND number is commonly received within two weeks of submission.

Questions and specific requests from the project manager may come during Weeks 3 and 4; similarly you may be alerted to exactly when the IND reviewing team will be gathering as a group and you may be asked to be ready to discuss matters with the reviewers. This meeting typically occurs around Day 28 or 29 of the 30-day review cycle. But you also have to be ready to receive an unannounced phone call at this time where the Division Director or the director's representative will inform you of the division's decision. Generally, this teleconference is not a time for negotiations; a decision has been made by the reviewing team, and the sponsor will have to abide by that decision.

The comments to the IND come in two categories. The first category will be forward-looking comments and recommendations intended to help the submitted protocol and beyond for consideration by the sponsor. The second category consists of comments which are "Clinical Hold" issues that, unless you agree to make changes right on the call, the FDA will inform you that your study cannot be conducted. An example would be a required protocol modification affecting your inclusion/exclusion criteria.

The FDA may also have "Partial Clinical Hold" requirements where the clinical study can proceed but not to the full extent as proposed in the IND. An example here would be that the agency will allow the low doses of a single, ascending dose study to proceed but will not allow higher doses to be used until further information is provided. A protocol amendment of either type does not necessarily delay your dosing date: file a protocol amended as per the FDA requests to the IND, and the protocol has immediate regulatory approval – there is no 30-day wait period for protocols filed to an approved IND. There is no official approval in writing from the FDA indicating the clinical study may proceed; therefore, an approved IND has no real meaning, resulting in the more common terminology of an "open" IND.

Even if there is no approval letter, the FDA will issue a written summary of the suggestions, comments, and requirements for the study to proceed within the next 4-7 working days. In cases of full or partial clinical hold, the FDA will provide their limitations as well as recommendations as to what the sponsor should do so that the hold may be lifted. The guiding regulations to clinical holds provided under 21CFR312.42 provide useful details on the timelines and requirements for managing clinical holds.⁶

Foreign data

The FDA is not likely to provide comments to non-clinical or manufacturing data simply on account of their foreign provenance. Other than the requirement that there be an open IND, there are generally no additional barriers to the importation of a drug intended for clinical investigations.

The situation can be somewhat different for clinical data where there are specific regulatory requirements which must be met. The requirements include that the study be conducted according to good clinical practices, which is loosely defined as a study following standards in the design, conduct, and reporting so that the agency has assurance that the reported results are credible and accurate. Review and approval by an Independent Ethics Committee and appropriate consenting of trial subjects should be considered of critical importance.

The acceptance of the foreign data will also be driven by the clinical protocol the foreign data are expected to support. The same foreign data set may be viewed differently if the proposed protocol

is an aggressive pivotal Phase III trial as compared to a conservative dose-ranging or drug-drug interaction study. Clarification of acceptance of foreign data is commonly a key question for the pre-IND meeting.

If the IND contains foreign clinical data, then the size of the IND can increase significantly from the typical 5 to 7 volumes for a First-in-Man IND to 60 volumes and more, since complete clinical study reports including all appendices need to be submitted. In this case, strong consideration should be given to submitting the IND as an electronic IND, as significant cost- and time-savings should be achieved (eg, a 60 volume IND will force the publishing and associated quality control of an estimated minimum of 120,000 pages of regulatory documents).

Maintenance phase

Once the IND is cleared, it has to be maintained. A regulatory log which lists all further submissions to the IND is essential. This log should include reference to meeting minutes, written contact reports summarising telephone conversations, and all submissions such as CMC updates, new clinical protocols, new reports from animal studies, safety updates, and the Annual Report.

Sometimes an IND is filed for strategic corporate reasons with no ensuing clinical activity in the US. With no submission or review fees by the FDA, prudence is suggested to maintain good relationships with the agency; frivolous IND submissions in the absence of sound corporate reasoning might impede the assistance you receive on other future submissions. Under any circumstance, the IND must be maintained over time by filing, at a minimum, Annual Reports to the IND. The purpose of the Annual Report is inform the FDA of

the drug's progress in development; however even if there has been no progress, an Annual Report to the IND must be filed in order to keep the IND open. If the IND is not maintained, then the FDA will eventually terminate the IND. If the IND is terminated and drug development starts again, then the entire IND would have to be refiled.

With the filing of your primary IND, you will receive comments from the FDA reviewers and understand exactly how the FDA views your drug with a forward-looking perspective to at least the next clinical study and probably beyond. Therefore, the stage is set to move effectively towards the ultimate goal of bringing your drug through clinical development to commercial approval, to provide help and assistance to patients in need of your product both in the US and elsewhere.

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