IDE Guidance #D99-1

Deputy Director for Science and Regulatory Policy
Office of Device Evaluation (HFZ-400)

Pre-IDE Program: Issues and Answers

ODE Review Staff

Purpose

This memorandum presents a discussion of issues and answers on the Pre-IDE program, as set forth in Blue Book Memorandum D95-1, entitled "Goals and Initiatives for the IDE Program," issued on July 12, 1995.

This memorandum reviews the intent of the Pre-IDE Program and outlines several cases for which a pre-IDE may be especially useful as opposed to a few cases where it may not be as helpful. The procedures for processing and reviewing this type of pre-submission are also revisited.

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MEMORANDUM

DATE: March 25, 1999

FROM: Deputy Director for Science and Regulatory Policy, ODE

TO: ODE Staff

SUBJECT: Pre-IDE Program: Issues and Answers

I. Introduction

In Blue Book Memorandum #D95-1 (http://www.fda.gov/cdrh/d951.html), the Pre-IDE Program was presented as a way for sponsors of investigational device exemptions (IDE) applications to be able to submit preliminary information for comment by the Office of Device Evaluation (ODE) before submitting the formal IDE application. Under this program, sponsors could elect to submit those sections of the IDE application (e.g., clinical protocol design, pre-clinical testing, etc) for which they wished to obtain FDA guidance, while preparing the remainder of the IDE application. It was anticipated that this program would allow ODE staff to provide early input to the device industry on specific aspects of the IDE application before the document was officially submitted while at the same time providing FDA staff with a "heads-up" on the investigational technology and/or clinical protocol.

Since the pre-IDE Program policy was issued in 1995, ODE has received and reviewed approximately 200 pre-IDEs per year. Although this program has been quite successful, issues have arisen that warrant further discussion. Questions such as when a pre-IDE is appropriate versus when the original IDE application should be submitted as well as what types of information should be submitted in a pre-IDE have come forward. In addition, ODE has received complaints from the device industry indicating that the pre-IDE process, in some instances, was so burdensome and time consuming as to jeopardize future participation in the Program. Other sponsors felt as if they were "locked' into the pre-IDE Program and could not submit the formal IDE application until all of the issues raised by the Agency were resolved. Therefore, in this memorandum, I would like to review the intent of the Program and outline several cases for which a pre-IDE may be especially useful as opposed to a few cases where it may not be as helpful. The procedures for processing and reviewing this type of pre-submission are also revisited.

II. Pre-IDE Program: What It Is and What It Is Not

To help clarify the intent of the Pre-IDE Program, a few key principles should be kept in mind. These are identified below:

1) First and foremost it should be stressed that the pre-IDE Program was primarily designed to benefit the IDE sponsor. By allowing the sponsor to obtain early Agency input on selected (by the sponsor) sections of the IDE application, it was hoped that the initiation of clinical trials would be facilitated.
2) In this same vein, it should be fully recognized that IDE sponsors have the option of submitting a pre-IDE; that is, pre-IDEs are never a prerequisite for an IDE.

3) The pre-IDE Program should be not be confused with the Early Collaboration or Determination provisions of sections 520 (g)(7) and 513(a)(3)(D), respectively, of the Food and Drug Administration Modernization Act of 1997 (http://www.fda.gov/cdrh/modact/earlymtg.pdf). Comments provided through the pre-IDE process are intended as informal input and are not in any way binding on the Agency or the sponsor as opposed to the new statutory provisions which have binding elements.

   It should also be noted that the pre-IDE Program was not intended to be a modular review program for IDE applications. That is, sponsors should recognize that even though the Agency may have already reviewed certain sections of an IDE through the pre-IDE process, this does not guarantee approval of the IDE or that additional questions may not arise during review of the formal IDE application.

4) The pre-IDE Program is not an in-depth review process. The Program was intended as a way for sponsors to obtain preliminary comments on their bench/animal testing and/or clinical protocol in a timely manner. It was not intended to be the detailed, comprehensive review that is conducted on an actual IDE application.

   In addition to the above, it should be emphasized that the pre-IDE Program is not a mechanism for sponsors to obtain advanced review of their pre-clinical data. Once an IDE sponsor has progressed to the point of actually collecting bench or animal data, the formal IDE application should be submitted rather than a pre-IDE.

5) The pre-IDE process was not meant to be burdensome to either the sponsor or the Agency. As discussed in more detail later in this memorandum, if IDE sponsors clearly identify those aspects on which they would like ODE reviewers to focus and ODE reviewers follow the established review procedures, the process should not be overly burdensome to either party.

6) The Pre-IDE process is not a way to identify and resolve disputes regarding the most appropriate bench/animal testing and/or clinical protocol design. Comment on pre-submissions is provided primarily by ODE review staff, not management. Thus, if IDE sponsors disagree with the advice provided through this process, resolution should be sought by submission of the formal IDE as it is only through this type of application that an official Agency determination is made.

III. Pre-IDE Program: When is It Appropriate?

Although the Pre-IDE Program is a way for IDE sponsors to obtain early, informal input on an aspect of a future IDE application, there are circumstances for which submission of this type of application are more useful than others. Those situations for which a pre-IDE may be particularly useful are discussed below.Non-Significant Risk Studies

As stipulated in 21 CFR 812, non-significant risk (NSR) studies do not need FDA's approval to be conducted. For this reason, ODE is generally not involved in the design of the study or the development of the clinical protocol. For this type of study, however, a sponsor may choose to submit a pre-IDE to help identify deficiencies that could preclude approval of a future marketing application. In this case, the pre-IDE application could consist of the proposed study design, clinical protocol, and/or statistical plan, thus allowing ODE staff an opportunity to provide comment on these important factors before the study is conducted.

On-going Pre-clinical Testing

Pre-IDEs may also be useful when the IDE sponsor is still conducting bench/animal testing and would like Agency feedback on a clinical protocol. This pre-IDE scenario may be particularly helpful to the sponsor as the informal review could be performed while the pre-clinical testing is being conducted and thus the total preparation time for the IDE application would not be extended.

During Development of the Clinical Protocol

IDE sponsors may request guidance on the type of bench/animal testing before it is conducted to increase the likelihood that the testing will be adequate to support initiation of the clinical investigation. As in the previous case, advice on this issue could be obtained while the sponsor is developing their clinical protocol, so that submission of the formal IDE is not delayed.

IV. Pre-IDE Program: When Is It Not Appropriate?

In contrast to the above situations in which a pre-IDE would tend to be quite helpful to IDE sponsors, there are some circumstances for which such submissions may not be as useful. These are discussed below.

The IDE Application is Complete

Over the last few years, ODE has received some pre-IDEs for essentially complete IDE applications with an indication that the sponsor is ready to begin their clinical trial. This type of pre-IDE is not the best use of the sponsor's or the Agency's time and resources. Instead of delaying submission of the original IDE application, the sponsor should submit their formal IDE application.

The Sponsor is Committed to a Certain Testing and/or Clinical Protocol

Similarly, if an IDE sponsor believes that the most appropriate bench/animal testing and/or clinical protocol has been developed and is committed to it, the sponsor should submit the formal IDE application. Once a sponsor has reached this point in the process, submission of a pre-IDE serves little, if any, useful purpose.

Device Design, Indications for Use, and/or Study Design Are Not Well Characterized

Contrary to the situations described above in which IDE sponsors have submitted pre-IDEs too late in the process, ODE has also received pre-IDEs too early in the device development process. The Agency recognizes that during the course of a clinical investigation, modifications to both the device and the clinical protocol will need to be made. Before advice on the most appropriate type of pre-clinical testing needed for initiation of the trial can be provided, however, the device design and the indications for use must be fairly well developed. Similarly, if the sponsor is looking for help on the study design or clinical protocol but has not yet formulated the basics (i.e., decided upon the type of control and identified the primary and secondary endpoints), it will be difficult for ODE staff to provide meaningful comment. Therefore, it is recommended that IDE sponsors develop these sections of the IDE as much as possible before the pre-IDE is submitted.

V. Pre-IDE Program: Procedures

Sponsor Responsibilities

As discussed above, there are several situations for which submission of a pre-IDE is especially useful, such as when the sponsor is working on one part of the application and would like an informal review on another section. Comment on NSR studies may also be obtained through the Pre-IDE Program. Since pre-IDEs may be submitted for a variety of reasons, the IDE sponsor should:

1) Clearly state the reason for the submission and
2) Identify those areas on which the sponsor would like the Agency to focus.

For example, a sponsor may state that he/she is seeking input on the most appropriate animal model for their investigational device and ask that the Agency provide comment on their proposed model, endpoints, and follow-up for this testing. Alternatively, a sponsor could submit their proposed clinical protocol and identify issues such as the primary/secondary endpoints, follow-up, and control treatment as those areas for which advice is requested.

FDA Responsibilities

In Attachment A, Procedures for Pre-IDE Meetings and Submission, of Blue Book #D95-1, procedures were established to address the processing and review of pre-IDEs. These procedures are still in effect and should be reviewed by ODE staff. Reviewers should

note, however, that since that memorandum was issued, a pre-IDE database has been developed. Therefore, all pre-IDEs should now be logged into this database and assigned a pre-IDE number beginning with the letter "I" by the Document Mail Center (DMC). Upon log-in, a 60 day review period will automatically be calculated and added to the tracking sheet.

As discussed in the Blue Book Memorandum, comment on the pre-IDE submission may be provided via letter, telephone conferencing, face-to-face meeting, or facsimile. To facilitate both the expeditious review of and response to these applications, the Agency encourages communication between ODE staff and the IDE sponsor in whatever manner allows the best resolution of the issues. It should be recognized that this will most likely involve more than one method of communication. For example, ODE staff may discuss the submission with the pre-IDE sponsor during a conference call but should still follow-up with either minutes of the meeting or written comments on the pre-IDE.

Upon log-out of the document, ODE staff is reminded that the application cannot be officially logged out without completion of the tracking sheet, including an indication of how feedback was provided to the sponsor and the date(s) that it occurred. Copies of all review memoranda, meeting minutes, or letters must be included in the pre-IDE before it is returned to the DMC.

Finally, when a formal IDE application is received, the number of any associated pre-IDE should be noted in the comment section of the IDE tracking sheet. This will allow the pre-original submission to be linked to the original IDE application and should facilitate review of the new submission.

/s/

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