Welcome to today's
FDA/CDRH Webinar

Thank you for your patience while we register all of today's participants.

If you have not connected to the audio portion of the webinar, please do so now:

Dial: 888-972-7807

Passcode: 1405152

FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigations

Owen Faris, Ph.D.
Clinical Trials Director (acting)
Office of Device Evaluation
Center for Devices and Radiological Health

Overview

- Streamlining clinical trials as an FDA Strategic Priority
- Define “Guidance” documents
- What is an Investigational Device Exemption (IDE) Study?
- History and original goals of this Guidance
- FDASIA Section 601
- What has changed in this Final Guidance compared to the Draft Guidance?
- Decisions for IDEs
- Information Communicated in FDA’s decision letters

FDA Strategic Priorities

- **CDRH has identified as a strategic priority the goal of improving US patient access to new devices by strengthening and streamlining the clinical trial enterprise so that medical device clinical trials are conducted in the US in an efficient, cost-effective manner, while maintaining appropriate patient protections.**
- **This guidance:**
  - Introduces processes to allow more efficient study enrollment to reduce the time and cost associated with the conduct of clinical trials;
  - Provides information regarding FDA's decision-making processes to improve predictability of the regulatory process; and
  - Introduces communications intended to improve the transparency of FDA's decision-making processes to study sponsors and other stakeholders.

FDA Guidance documents

- **An FDA guidance document:**
  - Explains FDA's current thinking on a topic
  - Does not establish legally enforceable responsibilities
  - Should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited

Investigational Device Exemption

- Established in section 520(g) of the FD&C Act and in 21 CFR Part 812
- FDA approval of an IDE is required for US human study of a significant risk device which is not approved or cleared for the indication being studied.
- Exempts sponsor from certain provisions of FD&C Act (e.g., requirement for a marketing application, compliance with full GMPs)
- Requirements for informed consent, labeling, monitoring of the study, records/reporting
- Initiation of the study requires approval by Institutional Review Board (IRB)

History of this Guidance

- Originally published as draft guidance on November 10, 2011
- Explained each of the possible FDA decisions
  - Approval
  - Approval with Conditions
  - Disapproval
- Provided examples of reasons that could support IDE Disapproval or Approval with Conditions
- Explained "Staged Approval," which allows some studies to begin while issues are addressed concurrently

FDASIA Section 601

Amends Section 520(g)(4)(C) of the FD&C Act

- **FDASIA became law on July 9, 2012**
- **FDA shall not disapprove an IDE because:**
  - the investigation may not support a substantial equivalence or de novo classification determination or approval of a device;
  - the investigation may not meet a requirement, including a data requirement, relating to the approval or clearance of a device; or
  - an additional or different investigation may be necessary to support clearance or approval of the device.

FDASIA Section 601

This means that an IDE cannot be disapproved on the basis of FDA's belief that the study design is inadequate to support a future PMA, 510(k), HDE, or de novo classification.

The standards for market approval (PMA/HDE) or clearance (510(k)) have not changed.

FDASIA Section 601

- **FDA implementation of the law included a working group to:**
  - Develop IDE decision policy
  - Modify IDE decision letter templates
  - Consider other mechanisms to encourage sponsors to work with FDA to develop pivotal trials that are appropriately designed to support marketing applications
  - Re-issue draft Guidance for public comment. (June, 2013)
  - Issue final Guidance

What is (nearly) unchanged from the draft Guidance?

- **Explanation of the reasons for which FDA may disapprove an IDE**
- **Explanation of mechanisms for approving IDEs**
  - Approval
  - Approval with Conditions
  - Staged Approval (some minor modifications for clarification)

What has changed from the draft Guidance?

- Changes to how Study Design Considerations and Future Considerations will be communicated to sponsors
- Removal of the proposal for a new voluntary, comprehensive, interactive review process to assist in the development of appropriately designed pivotal studies (Pre-Decisional IDE)
- These will be discussed in detail later in the talk

Possible FDA decisions for IDEs

- **Approval**
  - Approval of full study cohort
  - Staged Approval
- **Approval with Conditions**
  - Approval with Conditions of full study cohort
  - Staged Approval with Conditions
- **Disapproval**

Decisions: Approval

- FDA does not have remaining questions that must be addressed prior to enrollment of the approved number of subjects
- Study is approved for a specified number of enrolled subjects and investigational centers
- Study may be initiated upon IRB approval

Approval with Conditions

- FDA has determined that, despite some outstanding issues, the information provided is sufficient to justify human clinical evaluation of the device and the proposed study design is acceptable with regard to protection of study subjects.
- Resolution of those issues is not required prior to initiation of enrollment in the study, with the exception of certain issues related to the informed consent document (which must be corrected prior to enrollment)
- Sponsor may begin study upon receipt of IRB approval on the condition that, within 45 days from the date of FDA's decision letter, the sponsor submits information addressing the issues identified in FDA's letter.

Approval with Conditions

- Examples of typical Conditions:
  - Requests for additional information, data or changes that relate to protecting subjects in the study and can be addressed in a timely (45 days) manner but FDA determines do not need to be resolved prior to study initiation
  - Late stage follow-up procedures and assessments that relate to the care of study subjects but, because they occur late in the study, will likely be addressed prior to subjects reaching that point in the study
  - Minor issues related to the informed consent document that must be corrected before study initiation (i.e., subject enrollment) but can be reviewed by FDA after study initiation

Staged Approval

- Approval or Approval with Conditions is granted while certain outstanding questions are answered concurrently with enrollment of a limited number of subjects
- If the benefit-risk profile is sufficiently favorable to justify enrollment of a portion of the study subjects, a staged clinical investigation allows initiation of a study that might otherwise be disapproved while providing additional mitigation of risk by limiting exposure of the device to a smaller subject population
- The sponsor will be permitted to expand enrollment once an IDE supplement containing the necessary additional information is submitted to FDA and found to be acceptable.

Staged Approval

- May be appropriate when:
  - Additional clinical confirmation of the safety profile or the potential for benefit is obtained by reviewing initial data from subjects enrolled early in the clinical investigation before enrolling the entire subject cohort.
  - Additional confirmatory non-clinical testing is needed to more fully characterize device performance to adequately evaluate the potential risks of the device, before permitting testing of the entire subject cohort and is conducted concurrently with early enrollment in the clinical investigation.

Staged Approval

- Some additional considerations for pivotal studies:
  - Successful support of a marketing application under staged approval is not expected until the full planned cohort of subjects is studied.
  - A staged pivotal study should only be considered if the additional information that is requested is not expected to result in changes to important elements of the clinical investigation (e.g., endpoints, sample size, stopping rules) or device design.

Staged Approval

- Some additional considerations for pivotal studies:
  - FDA may determine that new feasibility data are needed prior to approval of the proposed pivotal IDE, in order to allow for a comprehensive examination of the study outcomes related to the device safety profile in a small group of subjects prior to exposing a large group of subjects to the risks of the study.
  - The data requested by FDA should not inappropriately unblind any of the relevant stakeholders, including the sponsor, investigators, or study management personnel, to critical study data.

Disapproval

Sponsor may not initiate the clinical investigation until the sponsor submits an amendment to the IDE to respond to the deficiencies identified in FDA's letter and subsequently receives a new letter from FDA granting approval or approval with conditions.

IDE disapproval and FDASIA Section 601

- Standards for protection of study subjects remain unchanged
- Issues regarding the study design that are not related to protecting study subjects are not the basis for a disapproval or approval with conditions decision

Disapproval

Consistent with 21 CFR 812.30(b) and section 520(g) of the FD&C Act, FDA may disapprove an IDE for any of the following reasons:

- There has been a failure to comply with any requirement in 21 CFR Part 812 or section 520(g) of the FD&C Act, any other applicable regulation or statute, or any condition of approval imposed by an IRB or FDA. (21 CFR 812.30(b)(1))
- The application or a report contains an untrue statement of material fact, or omits material information required by 21 CFR Part 812. (21 CFR 812.30(b)(2))
- The sponsor fails to respond to a request for additional information within the time prescribed by FDA. (21 CFR 812.30(b)(3))

Disapproval

- There is reason to believe that risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained (21 CFR 812.30(b)(4)), such as
  - Subject safety - investigational plan contains elements that would expose subjects to unacceptable probable risks, or fails to adequately protect study subjects from probable risks
- The informed consent requires changes to adequately inform subjects of the study, and must be reviewed by FDA prior to study initiation (21 CFR 812.30(b)(4))
- The investigation, as proposed, is scientifically unsound because it does not pose a reasonable scientific question or the investigation does not include the collection of data or information related to that scientific question (21 CFR 812.30(b)(4))
  - Note that "scientifically unsound" does not include concerns that the study design will not support a marketing application

Disapproval

- There is reason to believe that the device as used is ineffective (21 CFR 812.30(b)(4)), such as
  - Inadequate potential for benefit – available data suggest the device is ineffective or no information has been provided to suggest the device as used may result in patient benefit and the generation of knowledge adequate to justify the risks.
- It is otherwise unreasonable to begin or to continue the investigation owing to the way in which the device is used or the inadequacy of (i) the report of prior investigations or the investigational plan; (ii) the methods, facilities, and controls used for the manufacturing, processing, packaging, storage, and where appropriate, installation of the device; or (iii) monitoring and review of the investigation (21 CFR 812.30(b)(5), such as
  - Device safety – the data and information provided are insufficient to adequately characterize the safety profile of the device such that human clinical investigation is not considered reasonable

Additional detail and examples are provided in the Guidance

Study Design Considerations (SDCs)

- **FDA recommendations to a sponsor regarding changes that FDA believes should be made in order for the study to support its primary goals**
- **Examples include issues related to:**
  - Primary and major secondary endpoints
  - Randomization, control, and blinding
  - Follow-up duration and assessments
  - Statistical analysis plan
  - Enrollment criteria (if not related to subject protection)

Future Considerations (FCs)

- **Intended to provide helpful advice to sponsors regarding important elements of the future application that the IDE may not specifically address.**
- **Examples**
  - Known limitations of the IDE clinical investigation with regard to supporting certain claims or indications.
  - Specific non-clinical testing that, while not necessary to support approval of the IDE, will be needed to support the marketing application.

Communication of SDCs

- The draft guidance proposed that SDCs be included in a section of the IDE decision letter.
- FDA received comments from several stakeholders that proposed that FDA provide SDCs and FDA's assessment of the study design as a separate communication and not in the decision letter.
- Other stakeholders expressed support for inclusion of SDCs in the letter.
- Still others focused on ensuring that the decision letter clearly conveys whether or not FDA believes the study design is adequate to support its goals.

Communication of SDCs

- Based on the comments received, FDA believes that, when SDCs are included in the body of the decision letter, there is the potential for SDCs to be misinterpreted by sponsors and other stakeholders as issues that are required to be addressed.
- Therefore, FDA intends to convey SDCs in a separate attachment included with the decision letter, rather than in the body of the letter.
- The decision letter itself will state whether FDA believes that the study design is adequate to support the study goals or whether FDA recommends study design considerations in order for the study to do so.

Communication of SDCs

- If FDA recommends study design considerations, FDA's letter will note the following: "These recommendations do not relate to the safety, rights or welfare of study subjects and they do not need to be addressed in order for you to conduct your study."
- FDA will continue to engage with stakeholders on this issue and may make modifications to this approach in the future.

Communication of FCs

- FDA received comments proposing that the Agency provide future considerations as a separate communication and not in the decision letter.
- Based on the comments received, FDA intends to convey future considerations in a separate attachment included with the decision letter rather than in the body of the letter.

Removal of Pre-Decisional IDE

- The draft guidance proposed a new mechanism for review and interaction for pivotal IDEs called the Pre-Decisional IDE.
- The process included a comprehensive FDA review of a draft IDE prior to formal IDE submission, followed by written feedback from FDA and an interactive discussion between FDA and the sponsor.
- The goal of the Pre-Decisional IDE was to facilitate the development of an improved IDE submission that would be more likely to be approved, and include a study design that would be adequate to support a future marketing application.

Removal of Pre-Decisional IDE

- FDA received comments expressing concern that the Pre-Decisional IDE process itself might be too time consuming or require extensive FDA resources that could be better allocated elsewhere.
- FDA believes the Pre-submission process and other interaction mechanisms can address many of the same goals
- Based on the comments received and FDA's consideration of the points raised, FDA will not pursue the Pre-Decisional IDE at the present time.

How to find the guidance

- **To read the guidance, go to:**

  http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279107.pdf

Questions?

Owen Faris

owen.faris@fda.hhs.gov

Division of Industry and Consumer Education:
DICE@fda.hhs.gov

CDRHQuestions@fda.hhs.gov