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Client Alert

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FDA Issues Two Draft Guidance Documents Related to Investigational Device Exemptions

Agency Also Announces Pilot Program for IDEs for Early Feasibility Studies

On November 10, 2011, the Food and Drug Administration (FDA or the Agency) issued two draft guidance documents: *Investigational Device Exemptions (IDE) for Early Feasibility Medical Device Studies, Including Certain First in Human (FIH) Studies*,[i] and *FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigations*.[ii] The Agency also announced a small pilot program for implementation of the early feasibility study IDE draft guidance.[iii] Comments on the draft guidance documents must be submitted by February 8, 2012.[iv] FDA will begin accepting applications for the pilot program on December 12, 2011.

Early Feasibility Study IDE Draft Guidance

The early feasibility study draft guidance distinguishes early feasibility studies from traditional feasibility studies and pivotal studies. An early feasibility study is conducted using a medical device that is still in an early stage of development to generate data regarding the device's design concept with respect to basic safety and device functionality. On the other hand, a traditional feasibility study is usually conducted using a near-final or final device to obtain preliminary safety and effectiveness information.[v] Both types of feasibility studies differ from a pivotal study, which is intended to collect definitive evidence of safety and efficacy sufficient to support a marketing application.

The draft guidance identifies a pathway for the approval of investigational device exemptions (IDEs) for early feasibility studies for significant risk devices that is intended to make IDE requirements less onerous for sponsors of such studies. FDA expects this pathway to be used for "early clinical evaluations of medical devices to provide proof of principle and initial clinical safety data . . . when clinical experience is necessary because nonclinical testing methods are not available or adequate to provide the information needed to advance the developmental process."

In the draft guidance, FDA announces two new policy elements regarding the application for and approval of early feasibility study IDEs. First, FDA's approval of an IDE for an early feasibility study "may be based on less nonclinical data than would be expected for a traditional feasibility or a pivotal study." The draft guidance identifies the information that should be provided in IDE applications for early feasibility studies, including: (1) an explanation why an early feasibility study is appropriate; (2) a report of prior investigations that summarizes all relevant prior clinical, animal, and bench testing and that supports a finding that the device will function as intended, addresses basic device safety, and characterizes catastrophic failure modes and risk mitigation approaches; and (3) an investigation plan that addresses protection of human subjects, data monitoring, and risk mitigation. The draft guidance discusses the use of data monitoring committees for some early feasibility studies. FDA highly recommends the submission of a pre-IDE for early feasibility studies.

Second, FDA will institute the following "new approaches to facilitate timely device and clinical protocol modifications during an early feasibility study":

- The acceptance of 5-day notices for more types of modifications, including changes to the device and the investigational plan.
- The adoption of a contingent approval policy under which FDA and the sponsor will reach agreement about a nonclinical test plan and acceptance criteria that the sponsor will use to evaluate changes to the device or protocol. After agreement is reached, "FDA may approve the anticipated changes contingent on the sponsor's successful completion of the test plan, and the reporting of the test data to FDA within 10 calendar days of implementing the change."
- The use of an interactive review process when "the sponsor has completed nonclinical testing to evaluate device modifications, or whe[n] changes to the clinical protocol do not meet the criteria for a 5-day notice, and FDA decides that the additional information needed to address outstanding questions can be provided and reviewed within the 30-day cycle."

Pilot Program for Early Feasibility IDEs

To test and refine the procedures in the draft guidance, FDA announced a pilot program for early feasibility study IDEs. Candidates must meet the following criteria: (1) an IDE application has not yet been submitted; (2) the device's premarket application will require clinical data; and (3) nonclinical testing will not provide data needed for further development of the device and so limited clinical study (fewer than ten subjects) is necessary. Interested manufacturers should nominate their device for inclusion in the pilot program using the procedure specified in the Federal Register notice announcing the program.[vi] The program will be limited to nine candidates. FDA has not explained how it will choose the nine members of the pilot program if the Agency receives nominations from more than nine eligible candidates. FDA intends to inform the manufacturer whether the device has been accepted into the pilot program within 30 days of the Agency's receipt of the complete documentation. FDA intends to meet with the manufacturer within 30 days of the notification of the device's acceptance into the pilot program. The pilot program will end when FDA finalizes the early feasibility studies guidance.

IDE Decisions Draft Guidance

FDA has also issued a draft guidance document that identifies and describes the following IDE decisions:

- *Approval* - FDA will approve an IDE "when the IDE sponsor has submitted data and an adequate clinical investigation plan that support initiation of the study in humans." The sponsor may begin subject enrollment as long as the institutional review board (IRB) has approved the study.
- *Approval with Conditions* - FDA may issue an approval with conditions (previously called a conditional approval)[vii] when an IDE application has some outstanding issues that will need to be addressed, but "the information provided is sufficient to justify human clinical evaluation of the device, and that the proposed study design is generally acceptable." The sponsor may begin to enroll subjects in the study immediately upon IRB approval but must submit to FDA within 45 days a supplement to the IDE that addresses the issues identified in the approval with conditions letter. If FDA concludes that the response addresses the identified issues, the Agency will approve the IDE without conditions. If, however, issues remain, FDA will either issue another approval with conditions letter or withdraw the conditional approval.
- *Staged Approval or Staged Approval with Conditions* - Under a staged approval or staged approval with conditions, the clinical investigation may begin, but the initial stage of the study is limited to an identified subset of the planned subject enrollment. FDA will require the sponsor to conduct a parallel investigation or analysis of certain outstanding questions. The Agency expects that studies will continue uninterrupted beyond the first stage if the questions are addressed. FDA expects that staged approval and staged approval with conditions decisions will be more common for pivotal studies than for feasibility studies.
- *Disapproval* - FDA identifies three general reasons for disapproval of an IDE: (1) the data in the IDE application are "insufficient to adequately characterize the safety profile of the device"; (2) "[t]he potential risks of the proposed study are not justified"; or (3) "[t]he proposed study design or analysis plan is inadequate." The sponsor may not begin the proposed clinical study until FDA approves an IDE amendment that addresses the deficiencies.

In addition, FDA may identify future considerations in its approval, approval with conditions, or disapproval letters. The future considerations are topics that "FDA believes the sponsor should consider in preparation for a marketing application or a future clinical investigation." Examples include the effects of limitations of the IDE investigation on specific claims or indications or specific analyses that FDA will expect to see in the eventual marketing application. The IDE decisions draft guidance applies to decisions on IDEs for early feasibility studies, traditional feasibility studies and pivotal studies.

Implications for IDE Sponsors

FDA's early feasibility studies policy articulated in the draft guidance may make it more attractive for companies to conduct this type of feasibility study in the United States. However, the inclusion of only nine devices in the pilot program means that initially only a few companies will receive the potential benefits of FDA's new approach. Even after the pilot program is terminated and FDA finalizes the guidance, this approach will apply only to a small subset of feasibility studies. Moreover, the new distinction between "early" and "traditional" feasibility studies has the

potential to create confusion and delay in FDA's review and approval of an IDE if the Agency and the sponsor disagree on the characterization of the proposed study.

The draft IDE guidance suggests that FDA is reviving conditional and/or staged approvals and the identification of future considerations as IDE decision options. These options allow FDA to approve studies earlier, which means that companies should be able to start clinical studies sooner. If, however, IRBs wait to approve a study that has IDE approval with conditions until the Agency grants unconditional approval, then the start of the study will be delayed despite the nomenclature change. In addition, companies should pay careful attention to any issues for future consideration identified by FDA.

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King & Spalding will continue to monitor FDA developments regarding IDEs, including the issuance of the final versions of these draft guidance documents. If you have any questions about the IDE process, early feasibility studies or FDA's IDE decisions, please contact any of the authors of this Client Alert.

[i] Available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm277670.htm.
[ii] Available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm277669.htm
[iii] 76 Fed. Reg. 70152 (November 10, 2011), available at http://www.gpo.gov/fdsys/pkg/FR-2011-11-10/pdf/2011-29116.pdf.
[iv] Comments should be identified by Docket No. FDA-2011-D-0787 for the Early Feasibility Study IDE guidance and Docket No. FDA-2011-D-0790 for the FDA IDE Decisions guidance. Comments on both guidance documents may be submitted in writing to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Electronic comments may be submitted to http://www.regulations.gov.
[v] Both types of feasibility studies may, but need not, be first in human (FIH) studies.
[vi] 76 Fed. Reg. 70152 (November 10, 2011), available at http://www.gpo.gov/fdsys/pkg/FR-2011-11-10/pdf/2011-29116.pdf.
[vii] FDA explains that the terminology change is intended "to convey that the outstanding issues do not raise concerns that preclude FDA from granting approval for initiation of the clinical investigation."