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Client Alert

FDA & Life Sciences Practice Group

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FDA Issues Draft Guidance Regarding the Design of Pivotal Clinical Investigations of Medical Devices

Guidance Applicable to Clinical Studies in PMA and 510(k) Submissions

For more information, contact:

Edward M. Basile
+1 202 626 2903
ebasile@kslaw.com

Laurie A. Clarke
+1 202 626 2645
lclarke@kslaw.com

Beverly H. Lorell, M.D.
+1 202 383 8937
blorell@kslaw.com

Elaine H. Tseng
+1 415 318 1240
etseng@kslaw.com

Lynette A. Zentgraft
+1 202 626 2996
lzentgraft@kslaw.com

King & Spalding
Washington, D.C.
1700 Pennsylvania Avenue, NW
Washington, D.C. 20006-4707
Tel: +1 202 737 0500
Fax: +1 202 626 3737

San Francisco
101 Second Street
Suite 2300
San Francisco, CA 94105
Tel: +1 415 318 1200
Fax: +1 415 318 1300

www.kslaw.com

The Food and Drug Administration (FDA) issued a draft guidance on August 15 that sets forth the agency's recommendations regarding the design of pivotal clinical investigations of medical devices.[1] These recommendations are intended to help manufacturers and researchers design clinical investigations that satisfy premarket clinical data requirements. FDA's press release regarding this draft guidance[2] points out that its issuance is one of the 25 action items in the Agency's "*Plan of Action for Implementation of 510(k) and Science Recommendations*" (2011 Plan of Action).[3] The deadline for submitting public comments on the draft guidance is November 14, 2011.[4]

Three Stages of Medical Device Studies. In this draft guidance, FDA continues to divide the clinical development of medical devices into the following three stages: (1) the exploratory stage; (2) the pivotal stage; and (3) the postmarket stage. FDA explains that the exploratory stage includes first-in-human studies and feasibility/pilot studies, which the Agency defines as preliminary clinical studies to see if larger pivotal studies are practical and to refine the study protocols for the pivotal studies. In addition, FDA defines a medical device pivotal study as "a definitive study in which evidence is gathered to support the safety and effectiveness evaluation of the medical device for its intended use." The agency acknowledges that multiple pivotal studies of a device may be needed to answer different scientific questions. FDA does not define postmarket studies, but the Agency states that they include studies that are intended to better understand the safety of the device, including rare adverse events, and its long-term effectiveness.

Scope of the Draft Guidance. This draft guidance pertains only to pivotal studies. It focuses on the design of pivotal studies to support premarket approval (PMA) applications. It does not specifically address pivotal studies to support 510(k) notices. However, the draft guidance implies that it applies to such studies as it mentions the "least burdensome" requirements for both PMA and 510(k) submissions and acknowledges that in considering clinical trial design, the evidentiary burden should be commensurate with the "appropriate regulatory and scientific requirements." FDA's press release explicitly states that the draft guidance "may also be used in designing clinical studies used to support 510(k) submissions."[5] The draft guidance

does not apply to nonclinical studies, feasibility studies, postmarket studies, investigations intended to support Humanitarian Device Exemption submissions, studies of companion diagnostic devices that provide essential information for the development of companion therapeutic products, and studies of products regulated by the Center for Biological Evaluation and Research that require Investigational New Drug Application and Biologics License applications. FDA has publicly stated that it intends to issue a separate draft guidance regarding "first-in-man" feasibility studies.[6]

Purpose of the Draft Guidance. The draft guidance provides FDA's recommendations for determining study objectives, selecting the study design, minimizing bias and data variability, and choosing study participants and sites. According to Jeffrey Shuren, M.D., the Director of FDA's Center for Devices and Radiological Health, the draft guidance is intended to help medical device manufacturers design "better quality clinical studies."

FDA's Categorization of Devices and Studies. FDA divided devices into two broad categories based on their general intended uses: (1) therapeutic and aesthetic devices, which are "intended to treat a specific condition or disease" or to "provide a desired changes in the subject's appearance through physical modification of the structure of the body," respectively; and (2) diagnostic devices, which provide results "that are used alone or in the context of information to help assess a subject's target condition." In addition, FDA identified two categories of pivotal clinical studies: (1) clinical outcome studies in which subjects are assigned an intervention and then observed/tested at planned intervals using validated assessment tool to assess clinical outcome parameters or their validated surrogates to determine the safety and effectiveness of the intervention; and (2) diagnostic clinical performance studies that quantify how well the diagnostic device output agrees with the true target condition. In general, the clinical outcome studies are conducted on therapeutic and aesthetic devices and diagnostic clinical performance studies are conducted on diagnostic devices. However, clinical outcome study may be conducted on diagnostic device to evaluate the impact of the diagnosis on subjects' subsequent course of treatment or management by health care providers.

FDA's Recommendations Regarding Study Designs. FDA identified various possible study designs for both categories of pivotal studies and described their benefits and risks. FDA clearly considers double-masked, randomized, controlled, multi-center clinical studies to be the gold standard. However, FDA acknowledged that such testing may not be necessary or possible in certain situations, which the Agency identifies. FDA seemed to imply that manufacturers should justify any study design other than the gold standard.

The Significance of the Level of Risk Presented by the Study. FDA clarified that the Agency expects pivotal clinical studies to be scientifically rigorous and to yield robust data regardless of whether they are significant risk device studies that must comply with all of the applicable Investigational Device Exemption (IDE) requirements, nonsignificant risk device studies, which are subject to the abbreviated IDE requirements, or studies of devices that are exempt from IDE requirements. FDA encouraged device manufacturers to file pre-submissions containing pivotal study protocols to obtain the Agency's feedback on the study design even if FDA approval of an IDE is not required to conduct the study.

Potential Impact of the Draft Guidance on Device Manufacturers. The draft guidance reflects FDA's stated commitment to improve the quality and rigor of clinical investigations intended to support premarket submissions. FDA is likely to use this draft guidance to require that clinical data regarding the safety and effectiveness of devices provided in premarket submissions be scientifically valid. Therefore, manufacturers should consider following FDA's

recommendations regarding the design of clinical studies they intend to use to support PMA approval or 510(k) clearance of their devices.

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If you have questions regarding the draft guidance or if you want assistance in preparing and submitting comments on it, please contact us.

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[1] Accessible at, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm265553.htm
[2] Accessible at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm268000.htm
[3] Accessible at http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHReports/ucm239448.htm
[4] Comments should be identified by Docket No. FDA-2011-D-0567 and 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.
[5] Accessible at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm268000.htm
[6] William H. Maisel, MD, Deputy Director for Science, Office of the Center Director, Center for Devices and Radiological Health, FDA, speaking at Food and Drug Law Institute (FDLI) conference entitled, "An FDLI Dialogue: A First Look at the IOM Study of the 510(k) Clearance Process," August 4, 2011, Washington, D.C.