KING & SPALDING

Client Alert

FDA & Life Sciences Practice Group

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FDA Issues Proposed Rule Amending Regulations Regarding Acceptance of Data from Clinical Studies for Medical Devices

On February 25, 2013, the U.S. Food and Drug Administration (FDA) released a proposed rule entitled *Human Subject Protection: Acceptance of Data From Clinical Studies for Medical Devices*.[1] The proposed rule would require that clinical studies conducted outside the U.S. ("foreign clinical studies") provided in investigational device exemption applications (IDE) or premarket submissions, including 510(k), Premarket Approvals (PMA), Humanitarian Device Exemptions (HDE), and Product Development Protocols (PDP) submissions, comply with Good Clinical Practices (GCP) or provide a justification for not complying with the GCP requirements.[2] In addition, the proposed rule would require that clinical studies conducted inside the United States ("U.S. clinical studies") and provided in IDEs and premarket notifications (510(k) submissions) comply with the applicable provisions of FDA's existing regulations regarding the protection of human subjects, institutional review boards (IRBs), and IDE requirements as set forth in 21 C.F.R. Parts 50, 56, and 812, respectively. The proposed rule is intended to ensure the protection of human subjects and the integrity and quality of the data submitted. It is also intended to standardize the criteria for FDA's acceptance of clinical data in support of IDE and premarket submissions. Comments on the proposed rule must be submitted by May 28, 2013.[3]

I. Proposed Inclusion of Good Clinical Practice in the IDE Regulations

The proposed rule would incorporate the GCP requirements for acceptance of foreign clinical studies in FDA's investigational new drug application (IND) regulations into the IDE regulations by:

- Defining GCP in proposed 21 C.F.R. 812.28(a) as "*a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected";*

- Requiring the review and approval of the study by a Independent Ethics Committee (IEC), such as an IRB, prior to study initiation and obtaining and documenting the "*freely given*

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informed consent of the subject" (or legally authorized representative); and

- Identifying the specific circumstances when compliance with GCP does not require informed consent in life-threatening situations, consistent with the human subject protections and IRB regulations in Parts 50 and 56, respectively.

FDA's investigational new drug (IND) regulations currently include that definition of GCP and reflect those principles (see 21 C.F.R. 312.120).[4]

II. FDA's Acceptance of Data from Foreign Clinical Studies

FDA proposes to accept data from foreign clinical studies ("foreign clinical data") to support an IDE application and premarket submissions only if the studies were conducted in accordance with GCP or the study subjects' rights, safety and well-being, and the accuracy and credibility of the clinical data, were assured by other means. FDA would implement that requirement by amending the IDE regulations to identify the GCP requirements (as described above) and the 510(k) and PMA regulations to cross-reference those criteria. Under the proposed rule, the Agency would accept data from foreign clinical studies to support IDE and premarket submissions if the data are valid and the submissions contain the information required by the applicable IDE, 510(k), or PMA regulations, including:

- A statement that all foreign clinical studies were conducted in accordance with GCP or a brief explanation for any noncompliance and a description of the steps taken to "assure that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects were protected" (See proposed 21 C.F.R. 812.2(e), 812.27(b)(4)(ii), 812.28(a)(1), 807.87(j)(2), and 814.20(b)(6)(ii)(C));

- A statement that the data are available for FDA inspection (see proposed 21 C.F.R. 812.28(a)(1));

- "Supporting Information" regarding actions taken by the sponsor or applicant to ensure GCP conformance for each foreign study for which there is a statement that it was conducted in compliance with GCP (see proposed 21 C.F.R. 812.2(e)):

    - If the investigational product used in a foreign clinical study is a significant risk device (as defined in 21 C.F.R. 812.3), the "Supporting Information" consists of the items listed in proposed section 812.28(b), *e.g.*, a summary of the investigators' qualifications, a description of the research facilities, a detailed summary of the protocol and results, a summary of the IEC's decision to approve or modify the study, and a description of the investigators' GCP training; and

    - If the investigational product used in a foreign clinical study is a nonsignificant risk device or a device for which the study would have been exempt from IDE requirements under 21 C.F.R. 812.2(c) if it had been conducted in the U.S., the "Supporting Information" is a subset of the items required for a significant risk study described in proposed 812.28(b).

FDA also proposes to require that sponsors of foreign clinical studies, which are submitted in support of an IDE or marketing submission, retain the study records for a period of two years after the latter of the following: (1) the date on which the investigation is terminated or completed, or (2) the date that the records are no longer required to support a premarket submission. The proposed rule, if finalized, would harmonize FDA's criteria for accepting U.S. and foreign clinical data to support research and premarket submissions for drugs and devices.

III. FDA's Acceptance of Data from U.S. Clinical Studies

FDA proposes to amend the IDE and 510(k) regulations to specify the same requirements for accepting clinical data from U.S. studies as currently set forth in the PMA regulations (see 21 C.F.R. 814.20(b)(6)(ii)(A) and 21 C.F.R. 814.20(b)(6)(ii)(B)). HDE applications are subject to these existing PMA requirements (see 21 C.F.R. 814.104(b)(4)(i)). Specifically, FDA would require that 510(k) and IDE submissions include a statement that all studies were conducted in accordance with the informed consent, IRB, and IDE regulations in 21 C.F.R. Parts 50, 56, and 812, respectively. If a study were not conducted in compliance with these regulations, the submission must include a statement of the reason for noncompliance. Thus, the proposed rule, if FDA finalizes it, would ensure that U.S. clinical data provided in IDE and premarket submissions comply with these requirements.

IV. Non-Compliant Clinical Data

Report of prior investigations. The proposed rule would clarify that the Agency's current requirement that IDE, as well as PMA, HDE, and PDP, submissions include all relevant clinical data applies to data from foreign clinical studies even if the data were obtained from studies that were not GCP compliant (see proposed 21 C.F.R. 812.27(b)(4)(i) and 21 C.F.R. 814.20(b)(6)(ii)(C)). Specifically, the proposed rule would amend FDA's regulations to expressly provide that failure or the inability to comply with the GCP requirements for foreign clinical studies is not a justification for excluding those studies.

Denial or withdrawal of approval. The current regulations applicable to IDEs, PMAs, PDPs, and HDEs explicitly authorize the Agency to deny or withdraw approval of these four types of submissions if any U.S. clinical study described in them was not compliant with applicable FDA regulations (e.g., informed consent and IRB requirements under 21 C.F.R. Parts 50 and 56, respectively). In addition, current regulations permit denial or withdrawal of approval of PMAs, PDPs, and HDEs if "the rights or safety of human subjects were not adequately protected." (See 21 C.F.R. 814.45(a)(5) and 814.46(a)(4)). The proposed rule would also explicitly authorize FDA to deny or withdraw approval of IDE, PMA, PDP, and HDE submissions if "the supporting data [from non-compliant U.S. clinical studies] were determined to be otherwise unreliable." (See proposed 21 C.F.R. 814.45(a)(5) and 814.46(a)(4) and 21 C.F.R. 812. 30(b)(1)). In addition, the proposed rule would explicitly authorize the Agency to deny or withdraw approval of an IDE, PMA, PDP, or HDE if any foreign clinical study described in the submission was not compliant with the GCP requirements set forth in the proposed rule. (See proposed 21 C.F.R. 814.45(a)(5) and 814.46(a)(4)) and 21 C.F.R. 812. 30(b)(1)).

Notably, FDA's current regulations for 510(k)s do not expressly permit FDA to withdraw 510(k) clearance for similar reasons nor does the proposed rule seek to add any such authority to the 510(k) regulations.

V. Potential Impact on Medical Device Manufacturers.

- The proposed rule would, in essence, require foreign clinical studies used to support research and marketing submissions to comply with similar requirements regarding human subject protection and independent review as currently apply to U.S. clinical studies used for the same purpose. The proposed rule would also make the requirements for FDA acceptance of both U.S. and foreign clinical data consistent for all types of research and premarket submissions. Additionally, the proposed rule could place significant burdens on sponsors who conduct foreign clinical studies and applicants who plan to use data from such studies to support IDE and premarket submissions.

- The proposed rule expands the authority of the Agency to deny or withdraw approval of an IDE, PMA, PDP, or HDE based on non-compliant clinical data.

- The elements of GCP applicable to foreign studies in the proposed rule reference "auditing" as well as "monitoring." The proposed rule does not otherwise discuss auditing and the implications of the inclusion of auditing in the definition of GCP is not clear. There is currently not a requirement for sponsors of either U.S. or foreign clinical studies to conduct auditing and an internationally accepted guideline on GCP does not include an expectation that studies be audited.

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If you are interested in submitting comments to FDA regarding this proposed rule and would like assistance from King & Spalding, please let us know. We will continue to monitor developments related to this rulemaking.

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[1] 78 Fed. Reg. 12664 (Feb. 25, 2013).
[2] The proposed rule does not mention *de novo* requests regarding automatic Class III designation. We assume that it would apply to that type of premarket submission because one of the purposes of the proposed rule is to have consistent requirements regarding clinical data for all types of research and premarket submissions.
[3] Comments may be submitted by mail or electronically through Regulations.gov. and should identify docket number FDA-2013-N-0080.
[4] 73 Fed. Reg. 22,800 (April 28, 2009). The Investigational New Drug Application (IND) regulations codified at 21.C.F.R. 312.120 were amended in 2008 to define GCP and specify the conditions for acceptance of data from foreign clinical studies to support an IND or an application for marketing approval of a drug or biological product, including the requirement that the study "*was conducted in accordance with good clinical practice (GCP).*"