

# US FDA Publishes Proposed Rule on Non-US Clinical Studies

If the proposed rule on US FDA requirements for accepting data from medical device clinical studies conducted outside the United States becomes final, manufacturers will face significant new requirements.

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Currently, the US Premarket Approval (PMA) regulations in 21 *Code of Federal Regulations* Part 814 (21 *CFR* 814) include specific criteria for US FDA acceptance of non-US clinical study data. These criteria are in Section (Sec.) 814.15, Research conducted outside the United States, which specifies that if a clinical study conducted outside the United States is carried out under an Investigational Device Exemption (IDE), it must comply with the regulations in 21 *CFR* 812, Investigational Device Exemptions. If the study is not conducted under an IDE, it also specifies that the agency will accept data in support of a PMA if the data are valid and the clinical investigator has conducted the studies in conformance with the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever provides greater protection to the human subjects. If the standards of the country are used, the PMA applicant must describe any differences between those standards and the Declaration of Helsinki and explain why they offer greater protection to human subjects.

In addition, Sec. 814.15 provides for the submission of a PMA based solely on non-US clinical data if the non-US data are applicable to the US population and US medical practice, the studies have been performed by clinical investigators of recognised competence, and the data may be considered valid without the need for an on-site inspection by US FDA. If it considers such an inspection to be nec-

essary, the agency can validate the data through an on-site inspection or other appropriate means. The regulation also encourages PMA applicants to schedule a presubmission meeting with US FDA officials if approval is sought based solely on non-US clinical data.

In practice, US FDA has applied these same criteria to the acceptance of clinical study data in support of IDE applications and premarket notifications, also known as 510(k) submissions.

However, neither the regulations for premarket notifications (21 *CFR* 807) nor IDE regulations address the requirements for US FDA acceptance of data from clinical studies conducted outside the United States.

## Current requirements for US FDA acceptance of US clinical data

Sec. 814.20(6)(ii) of the PMA regulations requires that applications supported by clinical studies conducted in the United States include a statement that each study was conducted in compliance with institutional review board (IRB) regulations in 21 *CFR* 56, or was not subject to those regulations due to exemption or waiver, and that it was conducted in compliance with the informed consent regulations in 21 *CFR* 50. If the study was not conducted in compliance with these regulations, the application must include a brief statement of the reason for noncompliance. This section of the PMA regulations also requires a statement that each study was conducted in compliance with the IDE regulation con-



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cerning sponsors of clinical studies and clinical investigators. If the study was not conducted in compliance with IDE regulations, the applicant must explain the reason for noncompliance.

Neither the regulations for premarket notifications nor the IDE regulations address the requirements for US FDA acceptance of data from clinical studies conducted in the United States in support of a 510(k) submission or IDE application.

### Proposed regulations on acceptance of data from clinical studies

On 25 February 2013, US FDA published a proposal, "Human Subject Protection; Acceptance of Data from Clinical Studies for Medical Devices"<sup>1</sup> to amend its current regulations. The proposal describes revisions to the current requirements concerning clinical studies conducted both in and outside the United States, but the most significant impact would be on clinical studies conducted outside the United States. This is because US FDA is proposing to require that clinical studies conducted outside the United States in support of an IDE application, a 510(k) submission, a PMA application, a product development protocol (PDP) or a humanitarian device exemption (HDE) application be conducted in accordance with good clinical practice (GCP) and that documentation be developed to provide evidence that this has been done.

US FDA states that use of the term "clinical studies conducted outside the United States" is intended to address studies not conducted under an IDE and does not indicate a change in overall policy for device studies conducted outside the United States. Instead, the agency states that it needs to update its requirements to:

- reflect an evolution of the standards for protecting human subjects since the issuance of the PMA regulations in 1986,
- better ensure the quality and integrity of clinical data obtained from clinical studies conducted outside the United States,
- clarify requirements for US FDA acceptance of data from clinical studies in support of a 510(k) submission or IDE.

US FDA is also proposing to amend the 510(k) and IDE regulations to address requirements for acceptance of clinical data generated from clinical studies conducted in the United States.

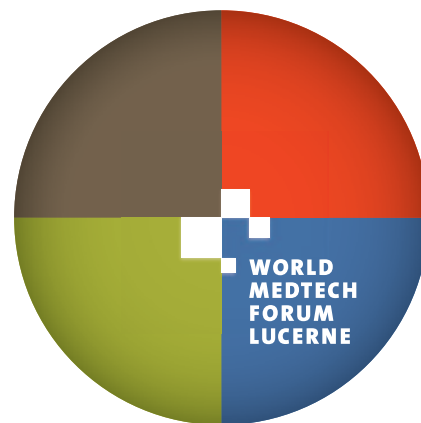
The period for accepting comments on the proposed rule ends on 28 May 2013. The effective date is proposed as 180 days after the final rule is published in the *Federal Register*.

### Clinical studies conducted outside the United States

US FDA is proposing to amend several provisions within the IDE regulation, including Sec. 812.2, Applicability; Sec. 812.3, Definitions; Sec. 812.27, Report of prior investigations; and Sec. 812.140, Records. The most significant revision, however, would be the addi-

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tion of proposed Sec. 812.28, Clinical studies conducted outside the United States, to address requirements for US FDA acceptance of data from non-US clinical studies. This is an entirely new section that was previously in the regulation only as a placeholder. Most of the proposed revisions are in this section.

Paragraph (a) of proposed Sec. 812.28 addresses requirements for the acceptance of data from clinical studies conducted outside the United States to support an IDE or device marketing application or submission. It indicates that US FDA will accept such data if:

- they are valid;
- supporting information specified in paragraph (b) of Sec. 812.28 and required elsewhere in 21 CFR 807, 812 and 814, as applicable, is submitted; and
- two statements are provided, one asserting that all such studies have been conducted in accordance with GCP, the other ensuring availability of the data from the study to US FDA for validation via onsite inspections or other appropriate means.

US FDA considers GCP 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. The agency believes that GCP includes review and approval (or provision of

a favourable opinion) by an independent ethics committee (IEC) before initiating a study and continuing review of an ongoing study by an IEC. It also requires manufacturers to obtain and document the freely given informed consent of the subject (or a subject's legally authorised representative, if the subject is unable to provide informed consent) before initiating a study.

Paragraph (b) of proposed Sec. 812.28 specifies the supporting information that a sponsor or applicant must provide to US FDA when submitting data from a clinical study conducted outside the United States in support of an IDE or device marketing application or submission. Readers should refer to the proposed rule for the full text of the proposed supporting information. However, briefly, this information may include all or a subset of the following:

- names and addresses of investigators and research facilities;
- investigator qualifications;
- description of research facilities;
- detailed summary of the protocol and results of the study;
- detailed information on any differences between the device used in the study conducted outside the United States compared with the device that is the subject of the submission or application;
- a discussion demonstrating that the data and information constitute valid scientific evidence (21 CFR 860.7), if the study is intended to support device safety and effectiveness;

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- name and address of the IEC and a statement that the IEC meets the definition in proposed Sec. 812.3(t);
- summary of the IEC's decision to approve (or modify and approve) the study or to provide a favourable opinion;
- description of how informed consent was obtained;
- description of what incentives, if any, were provided to subjects to participate in the study;
- description of how the sponsor monitored the study and ensured that it was carried out consistently with the study protocol; and
- description of how the investigators were trained to comply with GCP and to conduct the study in accordance with the study protocol, and a statement on whether written commitments by investigators to comply with GCP and the protocol were obtained.

Whether or not all or some of the information listed above is provided to US FDA will depend upon whether the medical device is considered a significant or nonsignificant risk device. Readers should refer to proposed Sec. 812.2, Applicability, for details of the proposed requirements for these two categories of devices.

### Potentially significant impact

Readers should review all the proposed amendments to 21 CFR 812, those concerning the premarket notification regulations in Sec.

807.87, Information required in a premarket notification submission, and the PMA regulations in Sec. 814.15, Research conducted outside the United States; Sec. 814.20, Application; Sec. 814.45, Denial of approval of a PMA; Sec. 814.46, Withdrawal of approval of a PMA; and Sec. 814.104, Original application.

This is a very important proposal for any company that, in the future, may need to conduct a clinical study to provide data in support of a US regulatory submission, in particular, with regard to clinical studies conducted outside the United States. For this reason, prudent companies will carefully review this far-reaching proposal and remain alert for news of its publication as a final rule.

### References

1. Human Subject Protection; Acceptance of Data from Clinical Studies for Medical Devices, US *Federal Register*, 78, 37, 25 February 2013; [www.gpo.gov/fdsys/pkg/FR-2013-02-25/pdf/2013-04201.pdf](http://www.gpo.gov/fdsys/pkg/FR-2013-02-25/pdf/2013-04201.pdf).

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