Updated regulations on FDA acceptance of medical device clinical data in effect soon

On 21 February 2018, FDA published a final rule[1] updating its regulations on the acceptance of clinical data generated outside or inside the United States (US), which are intended to support any type of medical device FDA application or submission. A previous article discussed the proposed rule[2]. This article will provide an overview of the updated regulations and a related guidance document published on the same date as the final rule.

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Effective date of the new regulations

Section III of the final rule specifies that the effective date of the rule is 21 February 2019. FDA explains that this means that the final rule will apply to all clinical investigations that enroll the first subject on or after 21 February 2019 and that support an investigational device exemption (IDE) or a device marketing application or submission to FDA. A subject is considered enrolled when the subject, or the subject's legally authorized representative, agrees to participate in a clinical investigation as indicated by the signing of the informed consent document(s), or participates in an investigation meeting the requirements of 21 CFR 50.24, which specifies exceptions from informed consent requirements for emergency research. The abbreviation "CFR" stands for Code of Federal Regulations.

Reason for updating the regulations

Until the publication of the final rule, the regulatory criteria for FDA acceptance of US and non-US clinical study data for medical devices were extremely limited and specified only in PMA regulations. In practice, FDA applied the acceptance criteria in the PMA regulations to clinical study data in support of IDE applications and premarket notifications as well. However, neither the premarket notification or IDE regulations addressed FDA acceptance of data from clinical investigations conducted outside the US.

Major provisions of the final rule

The requirements previously included only in PMA regulations on FDA acceptance of clinical data from investigations conducted in the US have now been added to the premarket notification and IDE regulations. For example, the new 21 CFR 807.87(j)(1) now requires a statement that each clinical investigation conducted in the US was conducted in compliance with applicable requirements related to the protection of human subjects and IRBs or was not subject to these regulations. If the investigation was not conducted in compliance with those regulations, a brief statement of the reason for noncompliance must be included in the submission. Similar requirements have been added to the IDE regulation in 21 CFR 812.27(b)(4)(i) and consistency ensured with modifications to the PMA regulation.

The most extensive changes to the regulations on FDA acceptance of clinical data in support of an application or submission, however, apply to clinical investigations conducted outside the US. These are included in a new section of the IDE regulations, 21 CFR 812.28, 'Acceptance of data from clinical investigations conducted outside the US'. In this section, FDA states that it will accept information on a clinical investigation conducted outside the US to support an IDE or a device marketing application or submission if the investigation is well-designed and well-conducted and specified conditions are met.

These conditions include the need for a statement that the investigation was conducted in accordance with good clinical practice (GCP), which is defined in the new regulation and is consistent with generally accepted principles of GCPs (see 21 CFR 812.28(a)(1)); references to the types of supporting information that must be submitted to FDA or maintained for agency review (see 21 CFR 812.28(a)(2)); and, ability for FDA to validate the data from the investigation through an onsite inspection, or through other appropriate means, if the agency deems it necessary (see 21 CFR 812.28(a)(3)).

The types of supporting information that must be submitted to FDA or maintained for agency review are described in 21 CFR 812.28(b) and depend on whether the clinical investigation is of a significant risk device[3], other than a significant risk device, or a device that meets the exemption criteria in 21 CFR 812.2(c). There are seven categories of exempted devices, such as a

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device that is undergoing consumer preference testing if the testing is not to determine safety or effectiveness and does not put subjects at risk.

All supporting information listed in 21 CFR 812.28(b) must be submitted to FDA when the clinical investigation is of a significant risk device, in brief, including the following:

(1) Names of the investigators and the names and addresses of the research facilities and sites where records relating to the investigation are maintained

(2) Investigator's qualifications

(3) Description of the research facility(ies)

(4) Detailed summary of the protocol and results of the investigation and, should FDA request, case records maintained by the investigator or additional background data, such as hospital or other institutional records (5) Statement concerning whether the device used in an investigation conducted outside the US is identical to the device that is the subject of the submission or application, or comprehensive information and comparisons made on any differences

(6) For an investigation intended to support device safety and effectiveness, a discussion demonstrating that the data and information constitute valid scientific evidence within the meaning of 21 CFR 860.7

(7) Name and address of the Independent Ethics Committee (IEC) that reviewed the investigation and a statement that the IEC meets the definition in 21 CFR 812.3(t). Records supporting such a statement and describing the qualifications of IEC members must be maintained and available for agency review

(8) Summary of the IEC's decision to approve or modify and approve the investigation, or to provide a favorable opinion

(9) Description of how informed consent was obtained

10) Description of what incentives, if any, were provided to subjects to participate in the investigation

(11) Description of how sponsor(s) monitored the investigation and ensured it was conducted consistent with the protocol

(12) Description of how investigators were trained to comply with GCP and conduct the investigation in accordance with the protocol, and a statement on whether written commitments by investigators to comply with GCP and the protocol were obtained.

In addition to the above, new sections have been added to 21 CFR 812.28(c) on obtaining waivers; 21 CFR 812.28(d) on the records required to be maintained; and, to 21 CFR 812.28(e) on clinical investigations conducted outside the US that do not meet conditions.

In addition, references to 21 CFR 812.28 are now included in relevant sections of the premarket notification regulations in 21 CFR 807.87, Information required in a premarket notification submission, and in PMA regulations in 21 CFR 814.15, 21 CFR 814.20 (Application), 814.45 (Denial of approval of a PMA), 21 CFR 814.46 (Withdrawal of approval of a PMA), and 21 CFR 814.104 (Original applications).

Helpful guidance on the new regulations

In addition to providing clarification on various aspects of the new regulations in the comments section of the final rule, FDA issued a guidance document[4] on the same day that the new regulation was published, which is in frequently asked questions format. The guidance document explains the requirements of the rule in plain language and how sponsors and applicants can comply with the requirements.

FDA rulemaking process and consideration of comments

Unlike the process in Europe, FDA publishes a proposed rule in the US Federal Register before the promulgation of regulations and provides interested parties an opportunity to submit comments. FDA then reviews the comments and takes them into consideration before issuing the final regulations and publishes a summary of the comments and FDA decisions as part of the Final Rule. On 25 February 2013, FDA published a proposed rule (78 FR 12664) on the acceptance of clinical study data in support of FDA applications or submissions and received comments from 7 medical device manufacturers, 2 from academia, 1 from a drug manufacturer, and 1 from a consumer. The FDA decisions taken as a result of the comments are interesting and summarized in Section II of the Final Rule and show that several important changes made to the proposed rule resulted from FDA's consideration of submitted comments. It is also interesting that certain FDA explanations and guidance related to a response to the submitted comments are also covered in the FAQ guidance document on the acceptance of clinical data.

Actions needed to ensure timely compliance

Manufacturers wishing to use the data from clinical investigations in any FDA application or submission will need to have a thorough understanding of the changes that have been introduced in the final rule on FDA acceptance of data from clinical investigations for medical devices. Once these changes are understood, it will be necessary to ensure correct implementation of the changes. This will include, among other activities, a revision of standard operating procedures and possibly work instructions, training on the new requirements, evaluation of study planning to ensure compliance with the new requirements, and ensuring that the new requirements will be considered when negotiating and contracting with study-related parties, not only for studies conducted outside the US, but also studies conducted in the US.

An important aspect of the new regulations will be the need to understand which information is to be maintained in case FDA requests it, or which must be submitted to FDA. This is important because a failure to submit required information may lead to an unfortunate delay in the FDA review process and affect overall project timelines. Prudent companies will ensure that necessary actions are taken to ensure compliance with the new regulations and thus help avoid any delay.

References

[1] Human Subject Protection; Acceptance of Data from Clinical Investigations for Medical Devices, US *Federal Register*, **83**(37), 21 February 2018

[2] M.E. Donawa, "US FDA Publishes Proposed Rule on Non-US Clinical Studies," European Medical Device Technology, **4**(3), 14-17, May/June 2013; can be downloaded from www.donawa.com, see "Free Articles", "US Regulatory Compliance"

[3] *Significant risk device* means an investigational device that: (1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; (2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; (3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. (21 CFR 812.3(m))

[4] Acceptance of Clinical Data to Support Medical Device Applications and Submissions, Frequently Asked Questions, Guidance for Industry and Food and Drug Administration Staff, US Food and Drug Administration, 21 February 2018. www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM597273.pdf

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