US Inspections of Clinical Investigation Sites

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If the United States (US) Food and Drug Administration (FDA) receives the funding that it has requested, it plans to increase inspections of clinical investigation sites both in the US and abroad. This article discusses US clinical investigation requirements and guidance documents that should be reviewed when preparing for FDA clinical site inspections.

FDA clinical study requirements

Unless exempt, clinical investigations conducted in the United States (US) must comply with the investigational device exemption (IDE) regulation in 21 Code of Federal Regulations (CFR) Part 812. This applies to clinical investigations conducted for providing safety and effectiveness data in support of a Premarket Approval (PMA) application or a Premarket Notification, also known as a 510(k) application, although most clinical investigations are conducted to support a PMA. The types of clinical investigations that do not need to meet the requirements of Part 812 are described in section 812.2(c), Exempted investigations. For example, Part 812 does not apply to a clinical investigation of a device that FDA has cleared for marketing that is used and studied in accordance with the indications for use examined by FDA during the review process. Readers should refer to section 812.2(c) to review other types of investigations that are also exempted from having to meet the requirements specified in Part 812.

The IDE regulation exempts devices intended solely for clinical investigation from having to comply with other Food, Drug and Cosmetic (FD&C) Act regulations that apply to commercially distributed devices. For example, while the device is under investigation, manufacturers do not have to register their establishments or list the device. In addition, except for design controls, they are exempt from the Quality System (QS) Regulation (21 CFR Part 820). In this article, the terms clinical investigation and clinical study are synonymous.

Compliance with the IDE regulation also includes compliance with other related regulations including

- 21 CFR Part 50, Protection of Human Subjects, which includes requirements for informed consent
- 21 CFR Part 56, Institutional Review Boards (IRBs), which oversee clinical investigation and in Europe are known as Ethics Committees
- 21 CFR Part 54, Financial Disclosure by Clinical Investigators
- 21 CFR Part 58, Good Laboratory Practices
- 21 CFR Part 820 Subpart C, Design Controls of the QS Regulation.

FDA maintains extensive information and guidance on these requirements on its website <www.fda.gov/cdrh>. In addition, information on IRBs and clinical investigations, some of which applies to medical devices, can be found at <www.fda.gov/oc/ohrt/irbs/default.htm>. Manufacturers should also be aware of the importance that FDA places on human factors considerations for IDE devices, which are explained in a guidance document.[1]

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→ FDA acceptance of nonUS clinical studies

Medical device clinical investigations conducted outside the US can be used in support of an application for marketing approval if certain conditions are met. The PMA regulations are found in 21 CFR Part 814, Section 814.15. Research conducted outside the US, specifies these conditions.

This section states that a study conducted outside the US under an IDE must comply with 21 CFR Part 812. It also states that FDA will accept studies conducted outside the US, but not conducted under an IDE, if the data are valid and if the investigator has conducted the studies in conformance with the Declaration of Helsinki or the 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 applicant must state in detail any differences between those standards and the Declaration of Helsinki and explain why they offer greater protection to the human subjects.

A PMA based solely on nonUS clinical data and otherwise meeting the criteria for approval under 21 CFR Part 814 may be approved providing FDA considers the nonUS data 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 FDA or, if FDA considers such an inspection to be necessary, FDA can validate the data through an on-site inspection or other appropriate means. This section states, however, that applicants are encouraged to meet with FDA officials in a "presubmission" meeting when approval based solely on nonUS data will be sought. Although these requirements are included in the PMA regulations, they are generally applicable to clinical studies conducted to support 510(k) submissions. Any doubt on the extent of this applicability should be discussed with FDA.

FDA investigators are instructed to identify outside services and contractors related to the study.

Bioresearch Monitoring Programme

The FDA bioresearch monitoring (BIMO) programme was established in 1977 as an agency-wide programme for monitoring studies involving FDA-regulated products. The programme for monitoring device-related studies is administered by the Center for Devices and Radiological Health (CDRH) Division of Bioresearch Monitoring (DBM). The objectives of the device programme are to ensure the quality and integrity of data and information submitted in applications to study, such as IDEs, and applications to market new devices, such as PMAs or 510(k)s, and the protection of human subjects taking part in studies from undue hazard or risk. In addition, DBM is responsible for the implementation of the FDA Application Integrity Policy (AIP) for devices and radiological health products, which is a programme for investigating sponsors suspected of submitting false or misleading data to FDA.

The objectives of the BIMO programme for medical devices are achieved by several means including

- audits of clinical data submitted in PMA and some 510(k) submissions
- audits of information included in IDE submissions
- inspections of nonclinical laboratories conducting device-related safety testing
- inspections of IRBs
- enforcement of the prohibition against commercialising investigational devices
- providing education, training and guidance to industry
- implementation of the AIP, previously mentioned.

Clinical site inspection programme and guidance

Clinical data audits are conducted during on-site inspections of clinical study sites. The inspection programme includes two types of inspections: routine inspections or directed inspections, which are sometimes referred to as "for cause" inspections. Routine inspections involve an evaluation of randomly selected sponsors, contract research organisations (CROs), monitors, clinical investigators, IRBs and laboratories that conduct animal or other

types of nonclinical testing. A sponsor is an individual or company that initiates clinical studies. A CRO is an organisation under contract to a sponsor to perform one or more of the sponsor's obligations. A monitor is an individual selected by a sponsor or CRO to oversee the clinical investigation. A clinical investigator actually conducts the clinical investigation or, if a team of individuals conducts the investigation, is the team leader.

Inspections conducted for reviewing the clinical data in a PMA are considered to be directed inspections. Directed inspections are also conducted because a problem has been identified during a review of a sponsor's submissions for ongoing IDE investigations, from the review of clinical data in a PMA or 510(k) submission, or from complaints from subjects, physicians or competitors.

Companies wishing to prepare for clinical site inspections should obtain the four Compliance Programme Guidance Manuals (CPGMs) that provide guidance to investigators on the manner in which they should conduct BIMO programme inspections. They also include information on the types of administrative procedures that should be followed and the regulatory enforcement actions that are possible. The manuals can be downloaded from the FDA website <www.fda.gov/ora/compliance_ref/bimo/ — Compliance Programs>. They include

- CPMG 7348.810, Sponsors, Contract Research Organisations and Monitors
- CPMG 7348.811, Clinical Investigators
- CPMG 7348.809, Institutional Review Boards
- CPMG 7348.808, Good Laboratory Practice (Nonclinical Laboratories).

CPMG 7348.810 for the inspection of sponsors, CROs and monitors states that FDA should not provide prenotification of the inspection. However, it is important to note that this policy does not apply in general to nonUS sites. This is because costly trips abroad could be scheduled only to subsequently find that the individuals needed for the inspection would not be available during the inspection. The manual states that the inspection should be based on a comparison of the commitments made in the IDE application and the actual procedures being followed by sponsors, monitors and CROs.

Detailed guidance is also provided on the types of documents that should be examined during the inspection, including organisational charts showing management of activities. FDA investigators are also instructed to identify outside services and contractors used, including CROs, monitors and others providing services related to the study. Therefore, it is important that all parties understand their obligations under the regulations being applied. Other areas that are evaluated during the inspection include the criteria used by the sponsor in selecting clinical investigators and monitors; the monitoring procedures and activities; the procedures for reporting unanticipated adverse experiences; the methods used for complying with electronic records and signature requirements; record retention practices; and methods used to control the investigational product. →

→ At the close of the inspection, any deviations from regulations that are identified during the inspection are provided in writing on Form FDA 483 and discussed with the responsible person at the site. Deviations from guidelines should not be included on Form FDA 483, but should be discussed with management and documented in the Establishment Inspection Report (EIR). The EIR is the detailed report of the inspection written by the FDA investigator after the inspection is completed. The EIR is reviewed and classified by DBM into one of three possible classifications based on the inspection findings:

- No Action Indicated (NAI) if no deviations or only minor deviations were identified
- Voluntary Action Indicated (VAI) if deviations requiring corrective actions were identified
- Official Action Indicated (OAI) if serious deviations were identified that could affect the safety of subjects and/or the validity of data submitted to FDA or serious violations identified during previous inspections were not corrected.

When serious deviations have been identified during the inspection, DBM will issue a Warning Letter requiring a written response from the recipient within a specified period of time. Warning Letters, excluding information that could be considered proprietary, are posted on the FDA website.

A detailed discussion of the remaining CPGMs is beyond the scope of this article. However, the inspection procedures in each manual are relatively similar in that the actual practices and procedures of the inspected party are compared with the commitments made in FDA submissions and applicable regulations. It should also be noted, that there are important differences among the four CPGMs. For this reason, companies conducting clinical investigations under an approved IDE should review each relevant CPGM and conduct audits to ensure that all parties are adequately prepared for possible on-site inspections. If clinical investigations are not being conducted under an approved IDE, companies should determine the criteria that FDA would use if inspections of these sites were conducted.

Reference

1. FDA, Center for Devices and Radiological Health, Human Factors Points to Consider for IDE Devices (undated). This document can be downloaded from the FDA website: www.fda.gov/cdrh/humfac/ide_hf.html or www.fda.gov/cdrh/humfac/ide_hf.pdf mdt

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