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Auditing Device Clinical Studies For US Requirements

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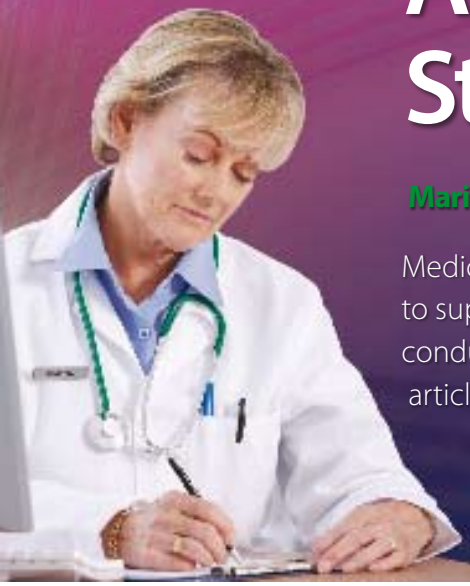
Medical device manufacturers conducting clinical studies outside the United States (US) to support US regulatory submissions should be prepared to show that these studies are conducted in a manner that will be acceptable to the Food and Drug Administration. This article discusses the audits that can be conducted to assess this acceptability.



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Usefulness of clinical study audits

Clinical studies are sometimes required for providing data to support medical device safety and performance claims during the process of placing these products on the market. These types of studies, especially those conducted at multiple clinical sites, which may be located in various countries, are expensive, time consuming and resource intensive. In addition, the conduct of clinical studies can have a critical impact on project timelines, because of the need to plan, organise and obtain the necessary approvals, screen and enroll subjects, and complete study follow-up.

For these reasons, all reasonable measures should be taken to ensure that clinical studies are conducted in conformity with good clinical practices (GCPs) and any applicable regulatory requirements and standards. In this way, the resulting data will be acceptable to regulatory bodies and other entities such as Notified Bodies that are involved in the evaluation of clinical data. Auditing sponsors, monitors, clinical sites and, where relevant, clinical research organisations (CROs) can be an extremely effective method for ensuring regulatory compliance, thereby increasing the likelihood of data acceptability.

It is important to stress that clinical study auditing by or on behalf of a study sponsor is not a specified requirement under United States (US) regulations or European requirements or standards for medical devices, although this type of audit activity is included in an international pharmaceutical GCP guidance document.[1] However, when clinical study data are used to support US regulatory submissions, the potential usefulness of a clinical study audit is important, and this is the subject of this article.

NonUS studies for US regulatory submissions

With increasing frequency medical device manufacturers are conducting clinical investigations outside the US. As discussed previously,[2] medical device clinical studies conducted outside the US can be used to support US regulatory submissions. For example, the regulations for submitting a US premarket approval application (PMA), which are found in 21 Code of Federal Regulations (CFR) Part 814, specify the conditions that must be met.

Section 814.15, Research Conducted Outside the United States, states that a study conducted outside the US under an Investigational Device Exemption (IDE) must comply with 21 CFR Part 812. It also states that the Food and Drug Administration (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 but otherwise meeting the criteria for approval under 21 CFR Part 814 may be approved providing:

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- 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
- the data may be considered valid without the need for an onsite inspection by FDA or, if FDA considers an inspection is necessary, FDA can validate the data through an onsite inspection or other appropriate means.

However, section 814.15(e) states that applicants are encouraged to meet with FDA officials in a "presubmission" meeting when approval based solely on foreign data is being sought. It is important to point out that these requirements are generally also applicable to clinical studies conducted to support 510(k) submissions. Nonetheless, it is advisable that companies discuss with FDA any doubts that they may have regarding the extent of this applicability.

Bioresearch monitoring programme

The FDA bioresearch monitoring (BIMO) programme was established in 1977 as an agency-wide plan for monitoring studies involving FDA-regulated products. The programme for monitoring device-related studies is administered by the Center for Devices and Radiological Health, 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 of applications to market new devices such as PMAs or 510(k)s
- the protection from undue hazard or risk of human subjects taking part in these studies.

In addition, DBM is responsible for the implementation of the FDA Application Integrity Policy for devices and radiological health products. This is a programme for investigating sponsors suspected of submitting false or misleading data to FDA.

BIMO is inspection-based, under which two types of inspections are conducted: routine inspections or directed inspections, the latter are also sometimes referred to as "for cause" inspections.

Routine inspections. These involve an evaluation of randomly selected sponsors, CROs, monitors, clinical investigators, institutional review boards and laboratories that conduct animal or other types of nonclinical testing. A sponsor is an individual or company that initiates a clinical study. A CRO is an organisation under contract to the 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.

Directed inspections. These are conducted for reviewing the clinical data in a PMA. 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 in response to complaints from subjects, physicians or competitors. ➔

➔ BIMO inspection of nonUS clinical sites

The BIMO programme includes the inspection of nonUS clinical sites, although the policy and procedures that FDA follows when inspecting these sites and limitations in FDA regulatory authority are not clearly stated in any publicly available FDA policy document.

For example, when BIMO inspections of nonUS IDE clinical study sites are conducted, FDA lacks the enforcement authority to issue an FDA Form 483 of inspection observations or a Warning Letter to these sites. The same limitation applies to the inspection of nonUS clinical sites conducting nonIDE studies. Instead, the results of BIMO inspections are included in written reports and recommendations, which are made to the appropriate FDA reviewing office, on the acceptability of the clinical data to support the regulatory submission in question. Therefore, any lack in FDA enforcement authority is more than compensated for by its power to reject or accept the clinical data generated by the clinical study that was the subject of the inspection. It is also important to recognise that if serious GCP problems are identified during a BIMO inspection of a nonUS clinical site, FDA may consider conducting an inspection of the sponsor if the sponsor is located in the US. In this case, FDA has the enforcement authority to issue an FDA Form 483 of inspection observations or a Warning Letter if serious violations of FDA clinical study requirements are identified.

Another factor that is extremely important regarding the conduct of BIMO inspections, both inside and outside the US, is that they are generally conducted when the clinical study has been completed. That is, they are data audits, which generally compare the commitments made in regulatory submissions with actual practices, procedures and original records related to the conduct of the study. At this point, it is generally too late to take corrective action to address the underlying cause of any serious violations that can affect the acceptability of the clinical data. This increases the importance of ensuring that clinical studies meet applicable US requirements and policies during the early stages of a clinical study when there is still time to prevent serious compliance problems from occurring.

Auditing for compliance with US requirements

Sponsors conducting clinical studies outside the US, whether or not the studies are being conducted under an IDE, should seriously consider conducting audits of these sites to assess compliance with US clinical study requirements and policies. These audits should be conducted as early as possible after initiation of the study to ensure that corrective actions can be made to eliminate any problems that could jeopardise the acceptability of the clinical data.

When considering this course of action, sponsors may believe this type of audit is unnecessary, because the clinical study is being monitored by qualified clinical research associates or others, who are responsible for performing the monitoring activity. However, the purpose of a clinical study audit extends beyond the monitoring activity. It should be viewed as an independent evaluation of clinical study activities and documents to determine whether the clinical study was conducted in accordance with GCPs, the sponsor's standard operating procedures and applicable regulatory requirements. In addition, the audit can also confirm that the clinical monitoring activity is being adequately conducted or it can identify deficiencies in this activity that can then be corrected.

Useful compliance manuals, auditing guidance and input

When clinical study audits are conducted in preparation for a possible BIMO inspection, the audit should evaluate the same areas that are covered in the FDA Compliance Programme Guidance Manuals (CPGMs). These provide guidance to BIMO investigators on the manner in which they should conduct BIMO inspections. The manuals can be downloaded from FDA's web site: www.fda.gov/ora/compliance_ref/bimo/Compliance Programs. The manuals that apply specifically to the points made in this article are CPMG 7348.810, Sponsors, Contract Research Organisations and Monitors; and CPMG 7348.811, Clinical Investigators.

The manuals provide detailed guidance on the types of documents that should be examined during a BIMO inspection, for example, organisational charts showing management of activities. FDA investigators are also instructed to identify the outside services and the contractors who are used, including CROs, monitors and others who provide services related to the study. 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
- methods used to control the investigational product.

Another source of valuable information regarding the types of problems that may be identified during BIMO inspections are the Warning Letters that are posted on FDA's website. Letters concerning nonUS clinical sites will not be found. However, the violations noted in the Warning Letters that are posted involving US clinical sites or sponsors are of the same nature as those that could be found during the inspection of a nonUS clinical site. Therefore, this information can be used to aid in the conduct of the audit.

Observe European standards

Prudent sponsors conducting clinical studies in Europe will ensure that the studies are conducted in conformity with the relevant European harmonised standards.[3,4] FDA participated in the development of these standards, which are based on established GCP practices and principles adapted to the needs of medical device clinical studies. Conformity with these standards will aid in compliance

with US requirements for clinical studies. It should also be noted that the newly revised ISO 14155-1, which is expected to be published in early 2009, includes a provision on clinical study auditing conducted by the sponsor or third parties designated by the sponsor.

References

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This article was first published in *Medical Device Technology*, vol. 18, no. 6, October 2007.