In Vitro Diagnostic Performance Evaluation Studies: Part 2

In vitro diagnostic medical devices are extremely important healthcare products for which performance evaluation studies can provide necessary evidence on safety and performance. Part 1 of this two-part article discussed European requirements related to performance evaluation studies. Part 2 discusses issues to consider when planning studies where results will be used not only for CE marking, but also for clearance or approval in the United States.

Design validation clarification

Part 1 of this article discussed the importance of distinguishing between performance evaluation studies and design validation, but it is important to point out that, under generally accepted quality system principles, performance evaluation studies are part of design validation. A better way of making this distinction is to say that performance evaluation studies are design validation studies conducted outside a manufacturer's premises under anticipated conditions of use of the product.

European and US terminology differences

The term "performance evaluation studies" is used for European IVD studies, as specified in the European In Vitro Diagnostic Medical Devices Directive (IVDD; 98/79/EC). By contrast, US FDA considers investigations with IVD medical devices as clinical studies regulated under the Investigational Device Exemption (IDE) regulation in Title 21 Code of Federal Regulations Part 812 (21 CFR 812), although many IVD studies are exempt from most of the provisions in this regulation.

For example, instead of "device for performance evaluation," US FDA refers to a device used in clinical studies as an "investigational device," whether or not it is an IVD or other type of medical device. In Section 812.3(g) of the IDE regulation, "Investigational device" is defined as "a device, including a transitional device, that is the object of an investigation." In Section 812.3(h) of the IDE regulation, "investigation" is defined as "a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device." No distinction is made between IVDs and other types of medical devices. This is important because European manufacturers may mistakenly believe that US regulations and requirements related to clinical studies do not apply to IVD studies involving patient samples when they are used to support safety and effectiveness, or safety and performance in the case of studies for CE marking purposes.

Determining IDE study exemptions

It is critical that any company considering the inclusion of a site in the United States for the conduct of an IVD study evaluate the IDE regulation and the extent to which it is applicable to the IVD study. US FDA guidance document, "In Vitro Diagnostic (IVD) Device Studies – Frequently Asked Questions," which can be downloaded from www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071230.pdf, was developed to provide general guidance on US IVD study requirements. In particular, it addresses IVD studies that are exempt from most of the requirements under the IDE regulation.

In response to the second question in the guidance document—How do I determine the applicability of the IDE regulaton to my IVD study?—it is suggested that readers begin with the exemptions in 21 CFR 812.2(c) of the IDE regulation. This explains that an IVD study is exempt from most requirements of the IDE regulation if the IVD device:

- is properly labeled in accordance with 21 CFR 809.10(c)
- is noninvasive (the meaning of noninvasive is given in 21 CFR 812.3(k), which specifies that simple venipuncture is considered noninvasive)

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- does not require an invasive sampling procedure that presents significant risk
- does not by design or intention introduce energy into a subject, and
- is not used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure.

Readers should refer to US FDA guidance for a complete discussion of these criteria.

Other US regulations covering IVD studies

In addition to the IDE regulation, some of the other regulations that may apply to IVD studies include:

- 21 CFR 50, Protection of Human Subjects
- 21 CFR 54, Financial Disclosure by Clinical Investigators
- 21 CFR 56, Institutional Review Boards
- 21 CFR 809, In Vitro Diagnostic Products for Human Use
- 21 CFR 11, Electronic Records; Electronic Signatures

It should be noted that the regulations for the Protection of Human Subjects and Institutional Review Boards apply to all clinical investigations regulated by US FDA under section 520(g) of the Food, Drug and Cosmetic Act. Therefore, all studies of investigational IVDs that will support applications to US FDA are subject to 21 CFR 50 and 21 CFR 56, even if they are not subject to most of the requirements of 21 CFR 812.

With regard to informed consent, the guidance document titled, "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that Are Not Individually Identifiable," explains that US FDA will exercise enforcement discretion with regard to informed consent requirements where IVD studies meet certain criteria, including the exemption criteria in 21 CFR 812.2(c), use of leftover specimens not individually identifiable and other criteria. Readers should refer to the guidance document for a complete explanation of this policy. It is available at www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm078384.htm.

The requirements for financial disclosure in 21 CFR Part 54 apply to those submitting a marketing application for a human drug, biological product or device and who submit "covered clinical studies." Readers should refer to the definition of "covered clinical study" in 21 CFR 54.2(e). The applicant must submit certification using Form FDA 3454, or disclosure statements using Form FDA 3455, where the applicant either contracted with one or more clinical investigators to conduct the studies or submitted studies conducted by others not under contract to the applicant.

ClinicalTrials.gov

In addition to the aforementioned regulations, it is useful to keep in mind that applicants of US regulatory submissions must comply with the requirements for the registration of clinical studies in ClinicalTrials.gov. That is, a provision of the US Public Health Service (PHS) Act, which went into effect on 26 December 2007, requires that a certification accompany certain human drug, biological prod-

uct, and device applications and submissions to US FDA indicating that the requirements of the new provision have been met. The purpose of the certification is to provide a means for ensuring that the public has access to information about certain clinical trials. Form FDA-3674, "Certification of Compliance with ClinicalTrials.gov Data Bank," is the form that is used to document compliance with the clinical study registration requirements. It is important to refer to the US FDA guidance document on the subject, available from www.fda.gov/RegulatoryInformation/Guidances/ucm125335.htm. It clarifies, for example, that under current US FDA policies, a certification is not required for 510(k) submissions that do not refer to, relate to or include information on or from a clinical study.

FDA guidance documents

Any manufacturer planning to use European performance evaluation study data in support of US applications or submissions should identify any applicable US FDA guidance documents that may have an effect on the study design. These guidance documents may be general or device-specific, and are listed on the US FDA website, www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070274.htm.

For example, guidance document "510(k) Submissions for Coagulation Instruments," issued on 19 June 2003, covers coagulation instruments (21 CFR 864.5400) and multipurpose systems for in vitro coagulation studies (21 CFR 864.5425). The guidance document recommends that the study device be evaluated in at least two external sites in addition to that of the manufacturer. Furthermore, performance should be assessed in the testing environment where the device ultimately will be used by individuals who will use the test in clinical practice, such as trained technologists.

An example of a more general guidance document on IVD devices, where the final result is qualitative, even if the underlying measurement is quantitative, is "Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests," issued on 13 March 2007. This is an important guidance document, available at www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071287.pdf, that provides advice on statistically appropriate practices for reporting results from studies evaluating qualitative diagnostic tests and practices considered inappropriate by US FDA.

US FDA–recognised standards

Before initiating IVD studies where the data will be used to support US applications or submissions, manufacturers should determine whether US FDA–recognised standards apply to the device being studied. This is also critically important because failure to comply with these standards can delay US FDA approval or clearance. At the time of writing, 100 standards are listed for the in vitro diagnostics product area, available at www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/results.cfm. Once a relevant standard is identified, it is important to review the standard's supplemental information, which can be accessed by clicking on the link. Supple-

mental information indicates the relevant CDRH offices and divisions associated with the standard, the devices covered by it, the affected application or submission processes, the extent of recognition of the standard and other useful information.

Pre-IDE process

The pre-IDE process is an informal presubmission process, which may involve the transmission of analytical or clinical protocols to US FDA for review and comment before proceeding with studies or questions on the regulatory pathway. In some cases, the process may involve telephone calls with the agency or even face-to-face meetings. The term pre-IDE has been used for this process so that US FDA can assign it an official tracking number, just as numbers are assigned to 510(k)s and PMAs. The process does not mean that manufacturers are required to subsequently submit an IDE application. Information on the circumstances under which it is appropriate to request a protocol review or a pre-IDE meeting is provided on the FDA website at www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm123682.htm.

BIMO programme

In addition to regulatory differences between the United States and Europe regarding the regulation of IVD studies using patient samples, another important difference is that US FDA conducts bioresearch monitoring (BIMO) inspections, which may include an evaluation of clinical investigators, sponsors, contract research organisations and monitors involved in IVD clinical studies. Information on FDA's BIMO programme is provided at www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm160670.htm. In addition to the general information on the BIMO programme, US FDA has developed a guidance document on BIMO inspections of IVDs, which can be downloaded from www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074893.htm.

European/US IVD study strategy

This article covers important considerations and checks that should be made by manufacturers intending to use European IVD performance evaluation study data to support US IVD applications or submissions. Depending on the particular IVD device, other important issues may need to be identified and addressed. The purpose of this article is to draw attention to the need to do this before costly and time-consuming performance evaluation studies are begun, so that needless duplication can be avoided.

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