In Vitro Diagnostic Performance Evaluation Studies: Part 1



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 discusses European requirements related to performance evaluation studies. Part 2 will discuss 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.

European definitions and implications

Article 1(e) of the European In Vitro Diagnostic Medical Devices Directive (IVDD; 98/79/EC) defines a "device for performance evaluation" as "any device intended by the manufacturer to be subject to one or more performance evaluation studies in laboratories for medical analyses or in other appropriate environments outside his own premises."

The term "performance evaluation" is not defined in the IVDD; however, it is defined in the European harmonised standard, EN 13612:2002, Performance evaluation of in vitro diagnostic medical devices. The standard states that "performance evaluation" means "investigation of the performance of an in vitro diagnostic medical device based upon data already available, scientific literature and/ or performance evaluation studies." The standard defines "performance evaluation studies" as "investigation of an in vitro diagnostic medical device intended to validate the performance claims under the anticipated conditions of use."

These are important definitions that help manufacturers determine whether they are conducting design validation or performance evaluation studies. For example, some companies believe they are conducting performance evaluations when, in fact, they are conducting design validation studies. Conducting tests with IVD reagents, instruments, controls or calibrators in the manufacturer's facilities, therefore, is not considered performance evaluation, but design validation. Design validation tests are intended to ensure that the IVD device is capable of meeting the requirements for a specified application or intended use. Performance evaluation studies are intended to validate the performance claims of the device under anticipated conditions of use, that is, how actual users are expected to use the device.

Evidence of performance claims

Section 3, indent 11 of Annex III, EC Declaration of Conformity, of the IVDD states that device technical documentation must include "adequate performance evaluation data showing the performances claimed by the manufacturer and supported by a reference measurement system (when available), with information on the reference methods, the reference materials, the known reference values, the accuracy and measurement units used; such data should originate from studies in a clinical or other appropriate environment or result from relevant biographical references."

In addition, section 6 of Annex III specifies requirements for selftesting devices, including the need to lodge an application for examination of the design of the device with a notified body. Section 6.1 requires, among other information, that test reports be submitted with the application including, where appropriate, results of studies carried out with lay persons and data showing the handling suitability of the device in view of its intended purpose for self-testing.

Section 3.2(c) of Annex IV, Full Quality Assurance System, requires that the quality system include all documentation referred to in Annex III, section 3, indents 3 to 13, which, of course, includes indent 11, mentioned above. Section 3 of Annex V, EC Type-Examination, requires that the same documentation be included in the application to the notified body for type examination.



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REGULATIONS AND STANDARDS

Thus, evidence of performance claims is required for all IVD devices; however, the particular IVD device and the risks associated with its use will determine whether the evaluation is based upon data already available, scientific literature and/or performance evaluation studies.

Requirements for performance evaluation studies

When manufacturers wish to conduct performance evaluation studies, they must comply with Article 9(4) of the IVDD, which requires that they follow the procedure referred to in Annex VIII, Statement and Procedures Concerning Devices for Performance Evaluation, and draw up the statement set out in that Annex before such devices are made available for the studies.

The IVDD does not require notification of the competent authorities in the countries where performance evaluation studies are being performed; however, national requirements for such a notification may exist, such as in Germany. Manufacturers should determine the existence of any national requirements for notification before study initiation. Instead of notification, the IVDD, in section 4 of Annex VIII, requires that devices for performance evaluation be registered with the competent authority of the country in which the manufacturer or authorised representative is established.

Essential requirement 8.4(f) of Annex I of the IVDD specifies that the label of devices for performance evaluation must include



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the words "for performance evaluation only." Manufacturers may wish to use the symbol for devices for performance evaluation as specified in the European harmonised standard, EN 980, Symbols for use in the labelling of medical devices, which will avoid the need for translations of "for performance evaluation only" into national languages.

Harmonised standards and technical specifications

As in the case of medical devices subject to the Medical Devices Directive (MDD; 93/42/EEC) and the Active Implantable Medical Devices Directive (AIMDD; 90/385/EEC), under Article 5, Reference to standards of the IVDD, member states must presume compliance with the essential requirements in Annex I of the IVDD for IVD devices in conformity with applicable European harmonised standards. The relevant harmonised standard for performance evaluation studies is EN 13612:2002, which will be discussed in more detail in Part 2 of this article.

Article 5 also requires that member states must presume compliance with the essential requirements for devices in conformity with common technical specifications (CTS) drawn up for the devices in List A of Annex II and, where necessary, the devices in List B of Annex II. At present, CTS have been developed only for devices in List A. CTS, which can be found on the European Commission website (http://ec.europa.eu/consumers/sectors/medical-devices/ documents/index_en.htm) establish performance evaluation and re-evaluation criteria, batch release criteria, reference methods and reference materials. Thus, CTS that have been developed for a particular device should be taken into consideration during the development of the performance evaluation study plan.

Statement for performance evaluations studies

Before initiating a performance evaluation study, the manufacturer or manufacturer's authorised representative must draw up a statement containing the information specified in section 2 of Annex VIII and ensure that any relevant provisions of the IVDD are met.

- Section 2 of Annex VIII requires the statement to contain:
- data allowing identification of the device in question
- an evaluation plan stating the purpose, scientific, technical or medical grounds, scope of the evaluation and number of devices concerned
- list of laboratories or other institutions taking part in the evaluation study
- starting date and scheduled duration of the evaluations and, in the case of devices for self-testing, the location and number of lay persons involved
- a statement that the device in question conforms to the requirements of the directive, apart from the aspects covered by the evaluation and apart from those specifically itemised in the statement, and that every precaution has been taken to protect the health and safety of the patient, user and other persons.

Other requirements in Annex VIII concern the retention of documentation that can be checked by competent authorities, and the required retention time, which is at least five years after the end of the performance evaluation.

Registration requirements

Section 4 of Annex VIII requires that certain provisions of Article 10, Registration of manufacturers and devices, must also be met for devices intended to be used for performance evaluation studies. These provisions are found in paragraphs 1, 3 and 5 of Article 10.

Paragraph 1 of Article 10 requires that any manufacturer who places devices on the market under his own name shall notify the competent authorities of the member state in which he has his registered place of business. Readers should refer to the article for the complete text of the requirements; however, some of the information that must be notified includes:

the address of the manufacturer's registered place of business

- information relating to the reagents, reagent products and calibration and control materials in terms of common technological characteristics and/or analytes and of any significant change thereto including discontinuation of placing on the market; for other devices, the appropriate indications
- in the case of devices covered by Annex II and of devices for self-testing, all data allowing for identification of such devices and other specified information including the outcome of performance evaluation pursuant to Annex VIII

Paragraph 3 of Article 10 requires that where a manufacturer who places devices on the market under his own name does not have a registered place of business in a member state, he shall designate an authorised representative. The authorised representative shall notify the competent authorities of the member state in which he has his registered place of business of the information referred to in paragraph 1.

Paragraph 5 of Article 10 is addressed to member states, which are required to take all necessary measures to ensure that the notifications referred to in paragraphs 1 and 3 are registered immediately in the European databank. Some member states, such as the UK Medicines and Healthcare products Regulatory Agency, have issued guidance on the IVD registration process for IVDs intended for performance evaluation. (See the online version of this article at emdt.co.uk for links to the guidance documents.)

Performance evaluation study strategy

A performance evaluation study strategy should be based upon the intended safety and performance claims of the IVD medical device, its technical and analytical characteristics, the risks associated with the use of the device, intended sales configuration, the manufacturer's business and marketing objectives, and perhaps other factors depending upon the particular study project, such as target population or laboratory practices.

If an IVD will be marketed not only in Europe, but also in the United States, early consideration of requirements in both jurisdictions is necessary to avoid the risk of having to repeat IVD studies to meet US FDA requirements. (To be continued.)

