What You Need to Know About FDA IVD Test Requirements

European manufacturers of IVD medical devices with CE marking experience may face significant additional verification and validation test requirements when placing their products on the U.S. market.

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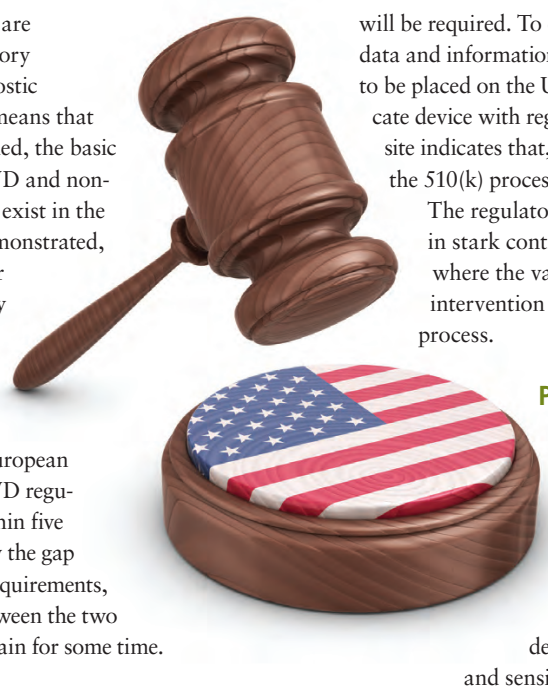
In vitro diagnostic devices (IVDs) are covered by the same FDA regulatory framework as non-in vitro diagnostic medical devices (non-IVDs). This means that once IVD classification is determined, the basic device regulations apply to both IVD and non-IVD devices. However, differences exist in the manner in which compliance is demonstrated, including the type of verification or validation studies needed to comply with FDA requirements.



In Europe, IVD medical devices are covered by the IVD Directive (98/79/EC; IVDD), developed under the European New Approach Resolution. New IVD regulations, due for implementation within five or six years, are expected to narrow the gap between U.S. and European IVD requirements, although significant differences between the two regulatory systems are likely to remain for some time.

IVD Classification

The classification of the IVD device determines the appropriate premarket process for FDA clearance or approval and also affects the extent of IVD testing required. As with non-IVD medical devices, FDA classifies IVDs as Class I, II, or III based upon the perceived level of regulatory control necessary to assure safety and effectiveness, with the lowest-risk devices in Class I and the highest in Class III.

IVD devices in Class I or II that are not exempt will require the clearance of a 510(k) premarket notification before being placed on the U.S. market. Class III devices will require a premarket approval (PMA) application unless the device is a preamendments device—on the market prior to 1976 or substantially equivalent to such a device—and FDA has not called for a PMA, in which case a 510(k) will be required. To obtain 510(k) clearance, companies must provide data and information to FDA to demonstrate that a device intended to be placed on the U.S. market is substantially equivalent to a predicate device with regard to safety and effectiveness. The FDA Web site indicates that, in 2013, 368 IVD devices were cleared through the 510(k) process and three PMAs were approved.

The regulatory oversight exercised by FDA over IVDs stands in stark contrast to the current European regulatory system, where the vast majority of IVDs require no evaluation or intervention by Notified Bodies during the CE marking process.

Premarket Testing Requirements

Most medical devices, including IVDs, enter the U.S. market through the 510(k) process. For IVDs, this process requires the evaluation of the analytical performance characteristics of the new device compared with the predicate device, including the bias or inaccuracy and imprecision of the new device, together with the analytical specificity and sensitivity. The agency aims to review 510(k) submissions in a 90-day timeframe; however, if additional information is requested, this timeline may increase.

In many cases, analytical studies using clinical samples will be sufficient. At times, study data can be supplemented by testing carefully selected artificial samples. FDA limits the use of this type of sample to a low percentage of total samples, however.

Clinical information may be required in other cases because the link between analytical performance and clinical performance is not well defined. For certain IVDs, FDA will request clinical samples with sufficient laboratory and/or clinical characterization to allow an assessment of the clinical validity of a new device. This is usually expressed in terms of clinical sensitivity and clinical specificity or agreement. If this is not considered sufficient, FDA may require prospective clinical studies.

The PMA approval process is much more rigorous than the 510(k) process, as it applies to the highest risk category of devices. FDA aims to review PMA submissions within 180 days; but, the process may take significantly longer if FDA identifies unaddressed scientific issues and requests additional information.

Analytical Performance

The studies needed to validate the analytical performance of an IVD will depend upon the type of IVD and whether it is, for example, qualitative, semiquantitative or quantitative. According to FDA, the major analytical performance parameters for IVDs may include: accuracy, limit of detection, limit of quantitation, analytical cut-off, precision, matrix comparison, analytical specificity (cross reactivity and interference), reagent and sample stability studies, reference interval, traceability to standard materials, linearity, method comparison, and high dose hook effect.

FDA will expect that validation study protocols provide information about the samples used for evaluation, the level of the analyte(s) being measured, study design, parameters to be assessed, acceptance criteria, and proposed methods for data analysis. Where analytical performance studies have been standardized, such as those described in Clinical and Laboratory Standards Institute (CLSI) standards, FDA will expect the studies to be based on such standards.

Expectations regarding analytical performance validation are defined in FDA standards and guidance documents, representing a further significant difference from the European system. This is because, apart from the European Common Technical Specifications that cover a very small number of products, there are 37 IVD harmonized standards listed on the European Commission Web site. Only one of these—EN 13612:2002, which is in need of significant revision—addresses IVD performance evaluation studies, however. In addition, there is no European-level guidance document on how to conduct IVD testing or address the technical issues covered by FDA-recognized standards and guidance documents.

Method Comparison

Method comparison studies generally compare the performance of the new device with the predicate device. For some device types, however, the appropriate comparator may be a reference method or clinical diagnosis. If there is no predicate device and an appropriate comparator needs to be selected, it is advisable that companies seek feedback from FDA through the agency's presubmission program before embarking on any studies.

When conducting method comparison studies, companies should be prepared to provide information to FDA on: study design, study population, method for sample size determination, study sample size, acceptance criteria, number of testing laboratory sites, criteria for sample type

selection and justification, method of sample collection and processing, the number of measurements recorded per individual (as applicable), the comparator or predicate device, testing protocols, and data analysis protocols.

Clinical Performance

The need to generate clinical performance data depends upon the type of device, its intended use, and other factors. For example, clinical data may be needed if the device is measuring or detecting a new analyte, has a new intended use or indications for use, or is based upon novel methodology. Clinical performance data are not required for many 510(k) submissions, but are generally required for PMAs, where device safety and effectiveness must be established. Clinical studies should not be confused with analytical studies that use clinical specimens to evaluate test measurement parameters compared with those of another method or device.

When clinical studies are conducted in the United States, study sponsors need to determine whether or not the IVD to be studied is subject to or exempt from the investigational device exemption (IDE) regulations specified in 21 CFR 812. An IDE allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data to support a PMA or 510(k) submission.

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Companies outside the United States should understand that, for most clinical studies, FDA will expect the studies to be conducted at a minimum of three different sites, with one or possibly more sites located in the country; however, this requirement will depend on the particular IVD. Even when test sites are outside of the United States, it will be necessary to demonstrate that the clinical data can be pooled.

Another important area where FDA places considerable emphasis concerns the statistical methods used to analyze test data. For example, FDA considers the statistical design of a clinical study in support of a U.S. premarket notification or application to be extremely important. Companies need to consult the FDA-recognized standards and guidance documents related to statistical analysis and the avoidance of bias early in the process of developing such data.

Presubmission Process

The FDA presubmission program provides companies with an opportunity to obtain FDA feedback before submitting premarket

notifications and applications. An FDA guidance document posted to the agency's Web site provides details of the program and the procedures that should be followed. FDA feedback may be provided in the form of a formal written response or a meeting or teleconference in which the feedback is documented in meeting minutes. The possibility to obtain FDA feedback is particularly important for ensuring that the company understands FDA expectations regarding testing to support a premarket submission before investing in costly and time-consuming test programs.

Standards and Guidance Documents

Identifying applicable FDA-recognized standards and guidance documents is one of the most important tasks that companies should undertake when deciding to enter the U.S. market in order to help prevent costly delays related to designs or testing that does not meet FDA requirements. FDA states in its guidance documents that they do not establish legally enforceable responsibilities. Instead, they describe the agency's current thinking on a topic and should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. Nevertheless, guidance documents should be consulted and, in most cases, followed, to avoid delays in device clearance or approval.

The FDA standards database can be searched to identify IVD-related standards, most of which are CLSI standards.

FDA guidance documents for IVDs can be found at the agency's Web site. It currently lists 128 IVD-related guidance documents, including general guidance, although many are product-specific. Product-specific guidance documents may cover such topics as precision evaluation studies, linearity evaluation studies, method comparison, interference evaluation, stability studies or other types of studies, depending upon the specific device.

Adequate Preparation Needed

The conduct of preclinical and clinical studies are generally the most time-consuming and costly activities when companies are planning to place their devices on the market. This also applies to IVD devices. In addition, the differences between the U.S. and European systems for regulating IVDs extend beyond the defined requirements for test data. Thus, prudent companies planning to enter the U.S. market should acquaint themselves with all FDA requirements, including test requirements, as early as possible in the development process.

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