REGULATORY FOCUS

Complying With the new EU IVDR

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This article discusses processes and plans that need to be developed by In Vitro Diagnostic (IVD) companies to address the new EU In Vitro Diagnostic Regulations (IVDRs) in advance of their coming into full force in 2022. Issues discussed include the differences between IVD and IVDR, new IVD classifications, notified bodies, new clinical evidence requirements and when to begin transitioning to the new requirements.

Introduction

On 5 May 2017, the *In Vitro Diagnostic Regulation* (*IVDR*) was published in the *Official Journal of the European Union* and the new regulations came into force on 25 May 2017. {1} While the full application of the new *IVDR* will occur on 26 May 2022, IVD companies planning to CE-mark their first product or continue to market their existing CE-marked products, should not wait until 2022 to transition. Companies should immediately begin developing and implementing strategies to be fully compliant with the changes, which will have complex and significant impacts on their development, clinical validation and commercialization plans. The impact to both existing and new IVD market authorizations and their launch plans includes stricter certifications for notified bodies (NB), more products being subject to premarket review, additional requirements for postmarket surveillance and establishment of clinical evidence for products that may have previously been subject to only analytical performance requirements.

Differences Between Current IVD Directive and new IVDR

The *In Vitro Diagnostic Medical Devices Directive* (*IVDD*) 98/79/EC was published in 1998 and has since been the governing document for companies seeking to market diagnostic devices in the European Economic Area.{2} The *IVDD* streamlined the process for making

products available to a broad European market without the requirement of country-specific approvals. At this time there were two methods for market entry: self-certification (about 80% of products) or NB approval (about 20% of products). Products subject to NB approval were limited to a series of specific products identified under Annex II, Lists A and B, and largely encompassed diagnostic products that are used in blood banking, devices for self-testing and certain infectious diseases.

The *IVDR* not only implements a formal regulation, it also repeals the *IVDD* over the course of the next five years. Why change the directive now? In the text of early articles of the regulation, the European Parliament and the Council of the European Union state, in part, that the *IVDR* establishes a "robust, transparent and sustainable regulatory framework for *in vitro* diagnostic medical devices that ensures a high level of safety and health whilst supporting innovation."

This statement implies, and boldly recognizes, that while the intent of the *IVDD* was to harmonize requirements across member countries, it did not provide the regulatory framework necessary for ensuring safe and effective products.

The IVD industry is of mixed opinion regarding this interpretation. Some would argue that the *IVDR increases* the regulatory burden and oversight of products not requiring such scrutiny, and as a result, innovation will be inhibited. Others argue the old *IVDD* was too lax and many products were placed on the market using an "honor system" of self-certification, which created opportunities to introduce and market unsafe and ineffective products.

Classifying Your IVD

The middle ground for *IVDR* lies in the use of a device classification system adopted by the Global Harmonization Task Force (GHTF){3} and later implemented under the International Medical Devices Regulators Forum (IMDRF).{4} The new device classification system transforms the requirements for placing products on the market from a two-class approach to a four-class, risk-based approach. This approach takes products previously classified under Annex II List A or B and "bundles" them under device classification D. More importantly, the *IVDR* takes the vast majority of self-certified products and reclassifies them into three new classes: C, B and A.

Products not previously specifically identified under the *IVDD*, such as companion diagnostics or standalone software products, are now included within the *IVDR* classification system. Even the elusive laboratory-developed tests or "home brew" tests are acknowledged under the *IVDR*. In addition to other requirements, they are only exempt from the regulation if no equivalent device is available on the market.

To illustrate, **Table 1** depicts a crosswalk showing the categorization of the product under the *IVDD* and its classification scheme under the *IVDR*.

Table 1. IVDD to IVDR Crosswalk

Example	IVDD	IVDR
Reagent for HIV 1and 2	List A	Class D and broadened to include "transmissible agent that could cause a life-threatening disease"
Reagents for determining PSA	List B	Class C and broadened to screening, diagnosis or staging of cancer
Genetic markers	Self-certified	Class C and covers all human genetic testing
Standalone software	Self-certified	Class C if independent from other devices and instruments
Software	Self-certified	If the software controls the instrument functions and/or results generation, it is classified in the same class as the instrument.
Cardiac markers, nonsignificant risk, infectious agent	Self-certified	Class B
Instruments, wash buffers	Self-certified	Class A (self-certified)

Why is reclassification important?

You and Your NB

Reclassification is important because products previously self-certified under the *IVDD* now require a level of NB review under the *IVDR*. Therefore, the vast majority of products (estimated to be ≥80%) will require NB review *before* they are placed on the market. And, the burden on NBs to be adequately trained and resourced to conduct comprehensive reviews of these products requires them to recertify under the *IVDR* and in some cases, to drop out of certain roles; for example, managing only class A-C products or drop out altogether. The European Association for Medical Devices of Notified Bodies or TEAM NB is one resource available for helping stay current on the NBs seeking certification to the *IVDR*.{5}

For those choosing an NB for the first time, the process for identifying the NB right for your company is not simply a task of choosing an NB from a published list. The chosen NB needs to match the type and classification of your product, demonstrate experience in your product area and have adequate resources to conduct the required product reviews in a timely manner. NBs with experience under the *IVDD* for Annex II List A or B products may be a good choice, as they have previous experience with technical reviews. Thoughtful and careful interviews with potential NBs should be undertaken before making this important choice.

Clinical Evidence Requirements

Reclassification is also important for IVD companies lacking experience in generating clinical evidence to support marketing their products. Now, manufacturers are required to have on file a clinical evidence report that includes scientific validity data, analytical performance data and clinical performance data, if applicable, based on the product's intended use. The report is a "living" document, similar to risk documents, and as such, requires review and updating throughout the product's lifecycle.

The GHTF has issued several documents to assist manufacturers in determining what IVD clinical evidence means and how it is studied.{6} Clinical evidence is used to support the marketing and labeling of the IVD, including claims made about the scientific validity and performance of the device, and most importantly to support any claim related to clinical utility. As the science changes over time, information documented in the clinical evidence report must be updated to address assay formulation and/or performance refinements and new publications adding information about the utility of the type of device. Similarly, information obtained through these and other postmarket surveillance activities may require manufacturers to update device labeling to remain current.

When to Transition From IVDD to IVDR

Thinking through when and how to transition existing products or preparing new products for entry to the European marketplace under *IVDR* should begin now. For manufacturers with products currently on the market, a gap assessment should be initiated to minimally identify: 1. the product's appropriate classification, 2. what clinical evidence is available to support the product, 3. when the current CE certificates expire and 4. what quality management system is used for conformity assessment. For manufacturers considering placement of new products on the market, it is still an option to market products under the *IVDD* for two to three years after the application of the *IVDR*. Because the NBs are not yet certified or widely in place under the new *IVDR*, it may now be too early to seek certification to the *IVDR*.

When placing a new product on the market under the *IVDD*, careful consideration should be given to the clinical evidence requirements for the future device's classification under the eventual *IVDR*. This is especially important for products that are self-certified under the current *IVDD*, but may require NB review under the *IVDR*. Manufacturers want to avoid having to backtrack from intended uses and using supporting clinical evidence that, under the *IVDD* would be broadly allowed, but under the *IVDR* may be subject to a narrower scope.

Preparing new product launches and continuing marketing current products can include the following steps:

- Review and prioritize the assays in the test portfolio to be submitted for review, based on business needs and technical criteria of the assays.
- Identify an NB for the future review process in anticipation of limited numbers of EU-certified NBs, and a logjam of premarket submissions for currently marketed assays.
- Prepare a list of the required analytical and clinical study data needed for a submission to an NB for each product.
- Evaluate readiness of the quality management system
- Make the hard decisions on assay discontinuation based on availability and/or quality of existing data, level of effort needed for new studies, and impact on business plans.

Conclusion

Once the *EU IVDR* is fully implemented, initial IVD launches in the EU may no longer be the norm. All product development and launch timelines will be gated by NB review, taking into account the time needed to prepare a formal NB submission that contains the required documents, the rate-limiting number of certified NBs and the likely possibility of large review backlogs caused by the large number of IVDs requiring NB review toward the end of the five-year period.

Executing a set of internal preparation steps in the five years between the *EU IVDR* publication and the full application will help IVD companies comply with the new requirements and pave the way for bringing their products to market in an efficient and timely manner. Moreover, beginning the process with currently marketed IVDs will provide a template and tested process for future IVDs that the company might bring to the EU market.

References

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