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GUIDE

IVDR Survival Guide:
Understanding the IVDR Product Classification System and Complying with the New Clinical Evidence and Performance Expectations

The EU has been working to strengthen its regulations for better patient protection and more effective implementation of the rules for in vitro diagnostic medical devices. As a result, in May 2017, a five-year in vitro diagnostic regulation (IVDR) transition plan went into effect. While some of the dates have been extended[1] to allow for the challenging nature of the transition from the old in vitro diagnostic medical devices directive (IVDD), the new IVDR officially applies as of May 26th, 2022.

Despite this long timeline, manufacturers still struggle to understand the IVDR requirements. This guide addresses common questions concerning the IVDR product classification system and how to comply with the new clinical evidence and performance expectations.

What distinguishes the IVDD from the IVDR?

Only a few requirements of IVDD are truly novel. Similarities include essential requirements, technical documentation and specifications, conformity assessment, registration, notified bodies, the European database EUDAMED, and vigilance.

Post-market surveillance was always necessary but has recently been upgraded. The same goes for unique device identification (UDI) now extended to Europe. In addition, the relationship among economic operators is changing slightly. For example, notified bodies (NBs) are now explicitly agents of the competent authority, and can't be as consultative as they were in the past.

Two completely new requirements for IVDR include: at least one person in the organization must be responsible for the company's regulatory compliance, and patients receiving genetic testing results must have access to counseling.

However, the main difference that will significantly affect compliance is the new, four-tier IVD classification system.

Despite the added work, the new IVDR is an improvement on the current directive. It is a more comprehensive approach that aligns the classification of IVD medical devices with other medical devices and international practice, as advocated by the Global Harmonization Task Force.

New, risk-based IVDR product classification system

Under the IVDR, a four-class system based on both patient and public health risk replaces the old IVDD two-class system:

Class	Patient Risk/Public Health Risk
D	High/High
C	High/Moderate
B	Moderate/Low
A	Low/Low

The most significant change is that, now, far more products fall into the higher risk groups and must be evaluated by NBs.

Who makes classification decisions?

Classifications are based on intended purpose. Manufacturers are responsible for demonstrating product performance and related scientific validity. They must also review the classification rules and determine the applicable class. Products falling under more than one risk category must be placed in the highest risk bracket. The NB will verify the correctness of the categorization and, if needed, the competent authority (CA) can be consulted to confirm classification.

A medical device coordination group has been established to implement and publish guidance and various documents to help explain and interpret the new rules. The Commission may also implement acts to help resolve issues of interpretation. Questions may arise as so many IVDs have never been subject to NB scrutiny before, and terms like “life-threatening” may be interpreted variously. If the manufacturer and NB disagree, the dispute may be referred to the relevant CAs.

The bottom line is that we must all be vigilant and monitor how such problems of interpretation are resolved through ongoing guidance and specific decisions.

How to know what to do for compliance now?

To determine your current level of compliance as well as next steps for each of your IVD devices, immediately:

1. Determine scope and device classification	2. Perform gap analysis against direct requirements	3. Develop transition strategy
▪ Look critically at your intended purpose and the performances for achieving that purpose ▪ Identify the risk class ▪ Examine the existing scientific and clinical evidence that supports the claimed performance	▪ Understand the new requirements for each product based on the new classification system ▪ Organize the relevant information and determine gaps	▪ Develop an action plan to fill the gaps in the new compliance requirements ▪ Secure an NB contract and agree with your NB on the product classification and implementation timeline

The key is to get started and have a plan in place. Even for a product that's been extended, this is a significant amount of work. For example, if you have to augment your clinical data package, you may need time to execute a full clinical trial. Do not delay.

Clinical evidence and performance requirements

Whereas clinical evidence was not needed for many IVD products in the past, manufacturers now need to show a legitimate level of product performance and clinical evidence, regardless of class.

What is acceptable clinical evidence under the IVDR?

Clinical evidence under the IVDR is clinical data and performance evaluation results. Is your dataset sufficient in quality and quantity to support your product and allow for a qualified assessment of whether the device achieves the intended clinical benefit and safety, when used as intended? This is now a requirement even for low-risk devices.

Data must be packaged such that the NB can assess it for validity, and it must include all supporting data that is available for review. Manufacturers must also determine and document how relevant the data is to the device in its current marketed form.

The process extends throughout the product life cycle. Data on the scientific validity information of the test, its analytical performance (limits of detection or quantification), and its clinical performance (demonstration that the test provides intended results) must be continually collected and reported to the authorities.

Performance evaluation reporting

All products now will require a performance evaluation report to verify the device's conformity with the general Safety Performance Requirements (Annex I). Driven by a Performance Evaluation Plan (Annex XIII) [2], performance evaluations must include:

- Intended purpose/intended use
- The analyte or marker
- Target populations
- A description of the state of the art
- How the performance evaluation is to be carried out, including acceptance criteria
- How to determine the acceptability of the benefit-risk ratio

This information is collated as a Performance Evaluation Report, the body of work that becomes the clinical evidence needed to conform to the IVDR requirements.

1. **Establishing scientific validity**
   There are many sources to establish scientific validity. For existing products, information may be gathered from peer-reviewed literature from databases such as PubMed, Embase, Cochrane, or Medline; relevant information from other devices; consensus expert opinions; or historical data and experience. At a minimum, plans should allow for prospective information gathering as the product continues to be used.

   For new devices/analytes, proof-of-concept or clinical studies may be required depending on the risk.

2. **Conducting analytical performance**
   Analytical performance is the ability of a device to detect or measure a particular analyte correctly. Bench studies to demonstrate this should account for the generally acknowledged state of the art. Use certified references and methods, such as clinical laboratory sciences institute or pharmacopeial standards. The IVDR expects a comparison to be made to a reference method to demonstrate the accuracy of the results. Consult the list of Analytical Performance parameters in IVDR Annex I 9.1.[2]

3. **Conducting clinical performance studies**
   Clinical performance studies demonstrate that the product works as expected for the target population and user. For certain lower-risk devices, reviews of published literature or experience gained from routine testing may suffice.

   However, for novel devices and markers and higher-risk products, comparison with a standard clinical practice or method comparator is necessary. This entails conducting a clinical performance study to establish the trueness of the value or the diagnostic accuracy.

Performance evaluation is a life-cycle approach

The Scientific Validity Report, Analytical Performance Report, and Clinical Performance Report are collated in the Performance Evaluation Report (PER). The PER must be updated throughout the life cycle of the device with new and factual data obtained from post-market performance follow-up and systematic post-market surveillance.

NBs will expect that manufacturers have a plan to review data at least annually for class C and D, or when necessary. For classes A and B, the low-risk devices, the PER is updated as necessary, but at least once every three years is recommended. This data must be assembled to allow a third-party notified body to verify conformity with the general safety performance requirements from Annex I. The goal is to ensure the product is working better than when it was first certified.

Understanding the IVDR requirements is half the challenge

Nearly all IVD manufacturers have questions about IVDR: “Do I have all the information necessary to support compliance? Is it organized in a way that allows for easy assessment?” Therefore, through their performance evaluations, manufacturers should thoroughly exhaust data sources to ensure they present the right level of information to demonstrate that the new requirements are being met.

Changes in device classification and the resultant escalation of third-party oversight, technical documentation requirements, quality management expectations, and economic operator responsibilities will all commandeer attention and resources.

It’s crucial to be proactive – and Premier can help. We are vigilant for new guidance and timelines. We can help you anticipate change and be proactive in meeting IVDR requirements. New guidance documents will evolve over the years, additional requirements may emerge, and timelines may shift. Consult our medical device experts, and be ready.

References

1. EUR-Lex. Regulation of the European Parliament and of the Council amending Regulation (EU) 2017/746 as regards transitional provisions for certain in vitro diagnostic medical devices and deferred application of requirements for in-house devices.
   Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52021PC0627&qid=1649009420749.
2. EUR-Lex. Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (Text with EEA relevance.)
   Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0746&qid=1649009099764.

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