IQVIA MEDTECH

Insight Brief

Understanding In Vitro Diagnostic (IVD) Risk-Based Classification in EU and US

Introduction

Are you an IVD manufacturer with your product on the market in the U.S. looking to scale your product into the European market? Are you in the process of transitioning your product to the European Union In Vitro Diagnostic Regulation (EU IVDR)? Have you considered the implications of the risk-based framework on the path to market for your IVD? There are many challenges faced by IVD manufacturers as they navigate the evolving global regulatory landscapes. Read more to examine the impact of the risk-based classification on manufacturers and gain insight to navigate the complexity of IVD regulations.

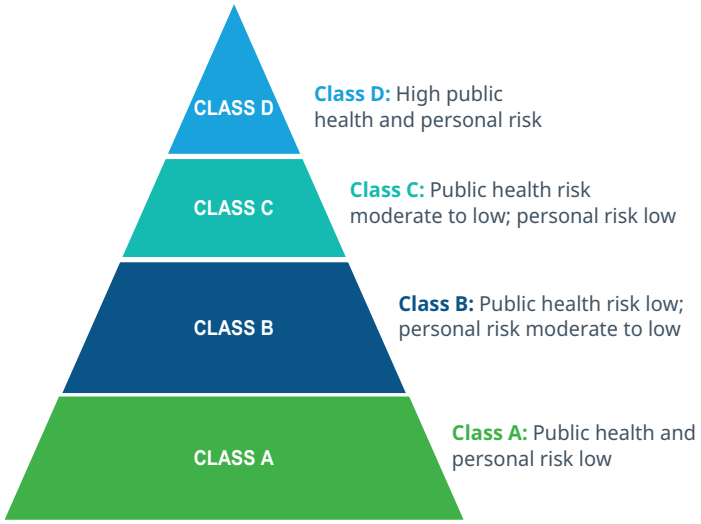
Current IVD regulatory environment: Transitioning to EU IVDR

Regulatory pathways to market approval vary by country. For instance, to place an IVD on the market in Europe, you must comply with IVDR, a risk-based framework that dictates the regulatory path these devices must follow. This framework also determines whether review by a notified body (NB) is necessary. As manufacturers strive to meet new requirements, transitioning from the In Vitro Diagnostic Directive (IVDD) to IVDR poses significant challenges, including the absence of product "grandfathering." While devices with a certificate issued in line with the IVDD can be marketed until May 26, 2025, those exempt from NB involvement can extend their market access until May 26, 2027, contingent on device classification. Compliance expectations and demands are intensifying, requiring additional clinical and analytical performance reporting requirements and adherence to an evolving regulatory landscape.

NOTIFIED BODY BOTTLENECK

Under the IVDD, only 10-20% of IVDs were subjected to NB oversight. In fact, many were self-certified and therefore required minimal NB involvement. Under IVDR, 80-90% of IVDs are now required to have a certificate, meaning that the NB will need to review the technical file but also the quality management system. Many devices that were previously self-certified (Class A) may need to be reclassified (Class B, C or D) according to the risk the IVD poses to patients. Meaning they will now have different levels of NB involvement depending on where their device falls within the classification scheme.

EU IVDR classification



As the manufacturer, you must identify the right risk class for your IVD device(s). Your NB will review if the classification is correct for Class B, C, D devices, and if you are executing pre-market clinical studies then your respective Competent Authorities (CA) may also verify your classification, even for Class A devices.

Since the date of application of the IVDR in May 2022, this has led to a bottleneck in NB capacity. As of June 2023, there were only 10 NBs approved to perform conformity assessment procedure under IVDR.

To overcome the NB bottleneck and help manufacturers in managing submission, the following transitional period was introduced for devices lawfully **placed on the market** under **IVDD before 26th May 2022:**

- 26 May 2025 for Class D devices;
- 26 May 2026 for Class C devices;
- 26 May 2027 for Class B devices;
- 26 May 2027 for Class A devices.

These transitional provisions are outlined in Article 110(4) of EU IVDR. In addition, the article removed the sell-off period to prevent unnecessary disposal of safe in vitro diagnostic medical devices that are still in the supply chain. In addition, the sell-off period for self-certified IVDs already placed on the market under the IVDD has been removed. These devices can be made further available on the market without legal time restrictions.

An illustrative case highlighting the need for re-classification of device families is found in Companion Diagnostics used for detecting the HER2 receptor for Trastuzumab treatment. Previously, these tests were not listed in the IVDD, and as a result, the tests required an EC Declaration of Conformity that did not need verification by a NB. However, under the IVDR, these tests are now classified as Class C products due to the moderate public health risk or a high individual risk that they pose. This classification is attributed to the risk associated if an erroneous false positive or false negative result occurs, leading to incorrect diagnosis and treatment.

In addition, IVDR includes higher requirements for clinical evidence, collection of clinical data and post market performance follow-ups. This is a big challenge for many manufacturers with legacy devices where sufficient data is not available or compliant with IVDR requirements. These new requirements have a significant impact for small- and medium-sized companies; it can be very resource intensive to fulfill the requirements for clinical evidence and post-market performance follow-ups.

A comparison of EU IVDR to U.S. FDA risk-based classification

When it comes to risk-based classification, a comparison emerges between the U.S. and EU classification systems for IVDs. Both the FDA IVD and EU IVDR enforce risk-based classification systems. In the U.S., the FDA recognizes ISO 14971:2019 as a consensus standard for risk management and device classification is also based on intended use or intended purpose as it is called in the IVDR.

While classification is based on the risk the device poses in both the U.S. and EU, notable distinctions surface when examining the classification criteria employed by each system. Unlike four levels of classification under EU IVDR, the FDA has only three levels of classification that can be assigned, which is Class 1 to Class 3. Class 1 is the lowest level of risk and Class 3 devices pose the greatest risk. Each classification has a different level of control necessary to assure the safety and effectiveness of the device.

Device classification plays a crucial role in determining pre-market submission requirements and potential quality system exemptions. For instance, a Class 1 device may be exempt from pre-market notification procedures, but if it is not exempt, a 510(k) submission is required for marketing clearance. The exemption status often depends on the device's intended use.

An example illuminates the impact of intended use on submission requirements. A typical cholesterol blood test conducted as part of a lipid panel during a medical checkup falls under Class 1 and receives exemption from pre-market notification procedures. However, an over-the-counter cholesterol test, also falling within Class 1, requires a 510(k) submission due to the additional risks associated with self-administration and interpretation by non-professionals.

The difference in regulatory requirements arises from the diverse levels of risk and the potential for errors when devices are used by individuals without professional training. Thus, despite yielding similar results, variations in how tests are administered and interpreted necessitate different levels of regulatory control.

The contrasting standards and the influence of intended use shed light on the importance of accurate device classification and regulatory oversight. It underscores the need for manufacturers to navigate these diverse frameworks to ensure compliance and facilitate market entry for their IVDs.

"Each classification has a different level of control necessary to assure the safety and effectiveness of the device."

Where to start? How can a manufacturer find out the classification of the IVD that they are developing?

TIPS FOR IVD RISK CLASSIFICATION & REGULATORY SUBMISSION

- Leverage existing FDA databases to help determine the U.S. regulatory pathway for your device. The FDA has a product code database which contains device names and their associated regulation number. If the manufacturer knows of an equivalent product, the manufacturer can look up that product in the database and obtain insight into that products device classification, whether the device is subject to general or special controls, and if the device is exempt from the premarket notification procedures.
- Determine the intended purpose of the device. A too broad intended purpose will result in being counterproductive due to the larger amount of clinical evidence that the manufacturer would need to collect to prove the device´s performance in achieving that intended purpose.
- Identify the applicable risk classification by reviewing the rules and determine which is the highest risk classification applicable and the related new compliance requirements.
- Ensure that the performance of the device and related scientific validity can be demonstrated. If you have an approved device in the U.S., chances are high you may have some of the required clinical evidence necessary for conformity assessment procedures.

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