

This publication is the third in a series of three that examines the new European Union (EU) regulations governing Medical Devices and *in vitro* Diagnostic Medical Devices (IVD). Focusing on the *in vitro* Diagnostic Medical Devices Regulation (IVDR),¹ this publication will examine the IVDR and focus on the IVD-specific provisions therein regarding classification, performance evaluations and clinical data, and conformity assessments. This publication will cover:

- The new ways IVDs will be classified, as well as an explanation of the classification rules
- An introduction to EU Reference Laboratories, which play an important role in IVD conformity assessments
- Short explanations of common items such as Unique Device Identifiers and Regulatory Enforcement Actions
- An explanation of performance evaluations
- An explanation of the conformity assessments for IVDs

Classification

In creating the IVDR, the European Commission made major changes with respect to how IVDs are classified in the EU. Under the current IVD Directive,² IVD reagents found in the two lists in Annex II and IVDs for self- and near-patient testing undergo conformity assessments that require a notified body. The manufacturer is able to self-certify all other IVDs that it manufactures. This self-certifiable group reportedly represents about 80% of all IVDs on the EU market, with only the other 20% of IVDs requiring notified body intervention. When the IVDR finally becomes applicable five years after its publication in the *Official Journal of the European Union*, this ratio will reportedly flip with 80% of all IVDs on the EU market requiring intervention from a notified body, and 20% remaining eligible for the manufacturer's self-certification. Understanding the changed classification scheme is the first step to determining what is required for an IVD to be successful in its conformity assessment.

There are four risk-based classes for IVDs under the IVDR, based on the Global Harmonization Task Force classification scheme: Classes A through D, with Class D IVDs testing for the highest risk conditions and diseases. An IVD's class is determined by following seven rules set out in Annex VII of the IVDR:

Class	Examples	Rules
A	Products for general laboratory use, buffer solutions, general culture media and histological stains, instruments for IVD procedures, and specimen receptacles	5
B	Self-testing devices for detecting pregnancy, fertility, cholesterol levels, glucose, erythrocytes, leucocytes and bacteria in urine; all other IVDs not otherwise classified; controls without a quantitative or qualitative assigned value	4, 6, 7
C	Devices intended to test for blood grouping or tissue typing for other markers, devices intended to detect presence of some infectious agents, companion diagnostics, infective disease status, disease staging, genetic testing, congenital disorder screening and others; self-testing devices	2, 3
D	IVDs used to detect the presence of transmissible agents in blood and organs to assess their suitability for transfusion, blood grouping or tissue typing tests used to determine markers for the ABO system, Rhesus, Kell, Kidd and Duffy systems	1, 2

Because a device's class drives many of the manufacturer's requirements for clinical evidence, performance evaluations and conformity assessments, correctly determining the device's class from the outset remains critical. IVD manufacturers should carefully assess their products with respect to the IVDR to determine the proper classification of their IVD.

¹ Harmonized Proposal for a Regulation of the European Parliament and of the Council on *in vitro* diagnostic medical devices (*Hereinafter* IVDR).

² Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices.

EU Reference Laboratories

EU Reference Laboratories are new regulatory actors introduced by the IVDR, and play a large role in the conformity assessments for IVDs. The European Commission designates EU Reference Laboratories to help assess specific devices, a category or group of devices or specific hazards related to a category or group of devices.³ With respect to IVDs, EU Reference Laboratories' role is to verify the claimed performances of Class D devices with the applicable Common Specifications, and carry out testing on samples of Class D IVDs.⁴

Unique Device Identifiers (UDI)

Unique Device Identifiers, or UDIs, are "a series of numeric or alphanumeric characters . . . created through internationally accepted device identification and coding standards and that allows unambiguous identification of specific devices on the market."⁵ In addition, the IVDR provides for a UDI Database to be established to validate, collate, process and make the core data elements for UDIs accessible to the public.⁶ For more information on the UDIs, we invite you to consult our first publication in this series.

Performance Evaluation

The Medical Devices Regulation (MDR) and IVDR share another major evolution in the increased need for more, and more robust, clinical and performance data. Specifically, the IVDR includes requirements for how the clinical and performance data may be obtained and minimum requirements to analyze the data for conformity. The IVDR states that the clinical evidence the manufacturer uses to support its device's intended purpose be "based on a continuous process of performance evaluation, following a performance evaluation plan."⁷ This clinical evidence is vital for the IVD's initial approval, as well as the IVD's continued conformity throughout its lifetime on the market. A performance evaluation is an "assessment and analysis of data to establish or verify the scientific validity, the analytical, and, where applicable, the clinical performance of a device."⁸ In other words, the performance evaluation is where the manufacturer analyzes and assesses the clinical and performance data it collects regarding its IVD, and establishes how its device conforms to the regulations, confirms its performance and confirms its risk-benefit ratio. Class C and D IVD performance evaluations, and the summaries of safety and performance, would need to be updated at least annually with the data that the manufacturer collects from its post-market surveillance.⁹

A manufacturer collects performance data by carrying out performance studies. According to the IVDR, performance studies must be carried out unless it is duly justified to rely on other sources of clinical performance data.¹⁰ Performance studies for IVDs, however, differ in important ways from clinical investigations for medical devices. To address these differences, Articles 48-58 of the IVDR contain provisions regarding conducting performance studies involving

taking samples in a surgically invasive manner, interventional clinical performance studies and if the conduct of the study involves invasive procedures or presents risks to the subjects.¹¹

Regulatory Enforcement Actions

The IVDR includes specific market enforcement duties for the new and existing regulatory operators. While notified bodies and competent authorities have regulatory duties regarding market access and surveillance, the IVDR includes provisions to close gaps among competent authorities' actions, reporting duties when taking actions against a manufacturer, and information sharing and cooperation. Additionally, the unannounced audits that some in the industry find contentious will be a permanent and explicit requirement of the manufacturer's conformity assessment.¹² For more information, we invite you to consult our first publication in this series.

Conformity Assessments

For IVD manufacturers newly accustomed to conformity assessments with a notified body, planning and preparation are key to ensure that the manufacturer and the product continue to have market access after the IVDR's application date. In other words, IVDs that do not conform to the requirements in the IVDR when the regulation is finally enforced may not be allowed to be on the market in the EU. In the IVDR, the conformity assessments for IVDs in Classes B, C and D require a notified body's intervention, a big difference from the current IVD directive, which requires only a small portion of IVDs to undergo a review from a notified body. For IVD manufacturers that do not currently work with a notified body, a notified body assesses the conformity of the medical device and the manufacturer's quality management system (QMS) through the conformity assessment the manufacturer chooses. Notified bodies generally assess the manufacturer's QMS and the device's technical documentation for conformity to the regulatory requirements. The manufacturer's QMS is examined, generally, to ensure that it will lead to the manufacture of conforming product. The technical documentation is how the manufacturer proves the device conforms to the Essential Requirements in Annex 1 of the IVDR. The manufacturer's QMS is what must produce the conforming device, and how the device conforms is shown through the technical documentation, so the conformity assessment includes both a review of the QMS and the technical documentation. Manufacturers may generally choose between the two conformity assessments depending on the structure of their QMS and company.

The main difference between the two conformity assessments is the scope of the QMS assessed. Manufacturers of Class A IVDs may still self-certify their products. It is important that the manufacturer weigh the choice of conformity assessment carefully to determine which is its most efficient option.

³ IVDR Art. 78(1).

⁴ Id. at Art. 78(2).

⁵ Id. at Article 2(12).

⁶ Id. at Article 22.1(d).

⁷ IVDR Art. 47(2).

⁸ Id. at Art. 2(35).

⁹ Id. at Art. 47(6).

¹⁰ IVDR at Art. 47(4).

¹¹ Id. at Art. 48aa(1).

¹² Id. at Annex VIII.4(4).

Annex VIII: Assessment Based on a Quality Management System and on Assessment of the Technical Documentation

In this conformity assessment, the notified body assesses the manufacturer's QMS and the device's technical documentation during audits as described in sections 3.3 and 4. Additionally, the notified body assesses the technical documentation of Classes D, C and B devices. Section 6 describes how the notified body will assess each class of device, including self-testing and near-patient testing IVDs. The manufacturer's entire QMS is assessed in this conformity assessment, including design and development.

Class D devices must also undergo batch verification. During batch verification, the notified body may ask an EU Reference Laboratory to verify the claimed performance and compliance of the IVD with the Common Specifications through laboratory testing.¹³ In addition, the technical documentation for IVDs for self-testing and near-patient testing in Classes B, C and D must be assessed. This technical documentation review is similar to a design dossier that Annex II List A IVDs currently undergo.

Annexes IX and X: Type Examination and Production Conformity Verification

The second conformity assessment choice is Annexes IX and X together, meaning the notified body uses the procedures in both Annexes IX and X to assess the conformity of the manufacturer's QMS (Annex X) and technical documentation (Annex IX). Annex IX, type examination, is generally a review of the technical documentation for the device type. Operationally, these reviews function in a similar way to technical documentation reviews for Class D devices. Additionally, Annex IX includes testing for when an EU Reference Laboratory is designated for a specific device undergoing review.

In terms of the QMS assessment, Annex X includes a review of the manufacturer's QMS for manufacturing and final inspection of the IVDs it manufactures.¹⁴ Annex X also requires the manufacturer examine each manufactured batch of IVDs to confirm its conformity with the technical documentation.¹⁵

Our lawyers have significant expertise advising clients on EU medical device and IVD regulatory issues. For more information about these regulations, or for help, contact your principal lawyer or any of the lawyers listed herein.

Contacts

Aline Doussin

T +44 207 655 1146

E aline.doussin@squirepb.com

Maren Ebner

T +49 69 1739 2448

E maren.ebner@squirepb.com

Joachim Heine

T +49 69 1739 2430

E joachim.heine@squirepb.com

Colleen Hermann

T +1 214 758 3402

E colleen.hermann@squirepb.com

Adrian Spooner

T +44 207 655 1067

E adrian.spooner@squirepb.com

Sarah Stec

T +1 202 457 6304

E sarah.stec@squirepb.com

John Wyand

T +1 202 626 6676

E john.wyand@squirepb.com

¹³ IVDR Annex VIII(5.7).

¹⁴ IVDR Annex X(1).

¹⁵ IVDR Annex X(5).