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White-paper

How Shimadzu is simplifying your compliance workload for the new IVD regulation!

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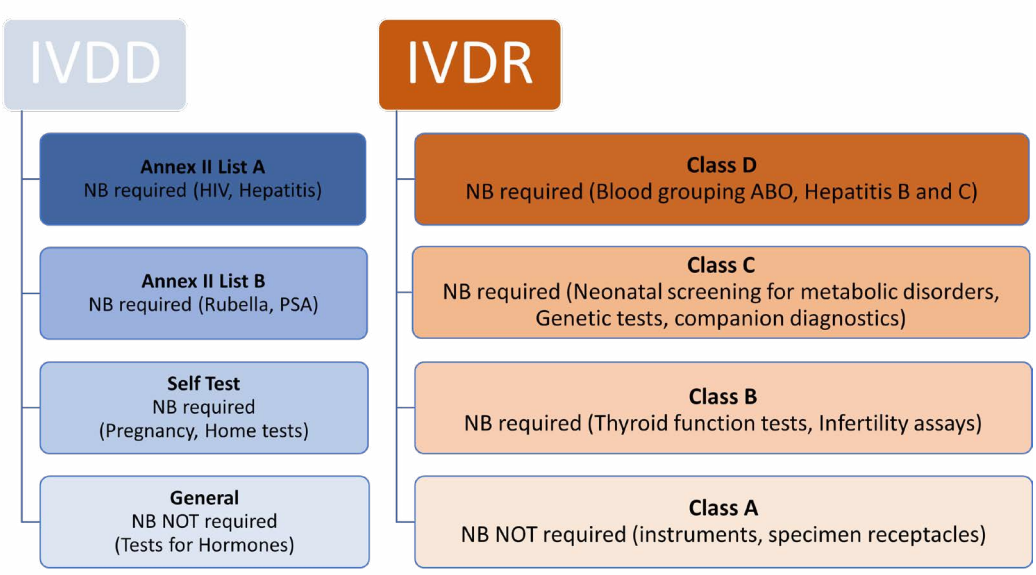
What is the New EU In Vitro Diagnostic Regulation (IVDR)?

New In Vitro Diagnostic Medical Device Regulation (IVDR) (EU) 2017/746 was published in EU Official Journal in May 2017 in order to ensure a high level of safety and health whilst supporting innovation. It applies from 26 May 2022 and replaced the previous IVD Directive (98/79/EC). This regulation set rules for in vitro diagnostic devices such as reagent, calibrator, kit, instrument, and software intended by the manufacturer to be used for diagnostic purposes.

IVDR retains some concepts of IVD Directive such as CE marking or essential requirements (under IVDR called "general safety and performance requirements"). As in the past, the manufacturers have to demonstrate that they and their devices meet the requirements through conformity assessment procedure.

Different from IVD Directive, however, IVDR introduced the risk-based classification (Figure 1). Under IVDR devices are classified in four: The devices with highest risks are classified in class D. The class A devices have low risks and include products for general laboratory use, accessories which possess no critical characteristics.



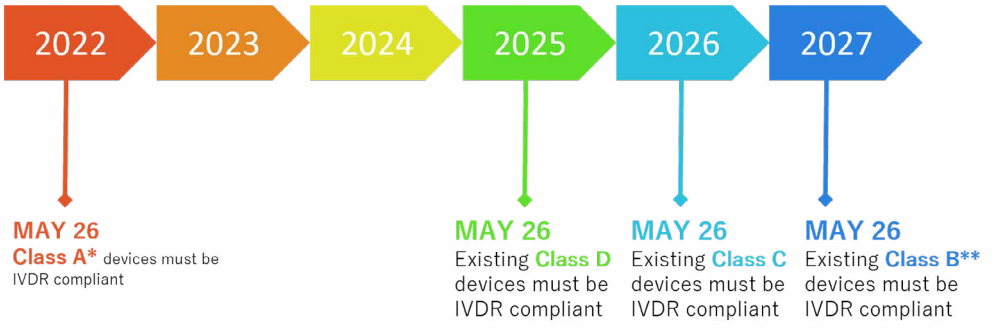
NB: Notified Body

Figure 1. IVDR risk-based classification

As shown Figure 2, self-declaration of conformity by the manufacturer which meet the requirements of IVDR is necessary to place the class A devices* on the EU market from 26 May 2022. Class B**, C, and D devices need the certification from the accredited Notified Body (NB) to be placed on the EU market. While only 8 % of devices required NB certification under the IVD Directive, 78 % of devices require NB certification under IVDR.[1] Despite the fact, the number of NBs accredited in the EU is small.[2] For that reason, in December 2021, the transition period has been postponed depending on the class (class B** until 26 May 2027, class C until 26 May 2026, and class D until 26 May 2025). The European Commission presented a further postponement proposal in January 2024.[3] If this amendment proposal is published in the official Journal as it is, the transition period of class B** devices will be postponed until 31 December 2029, class C until 31 December 2028 and class D until 31 December 2027.

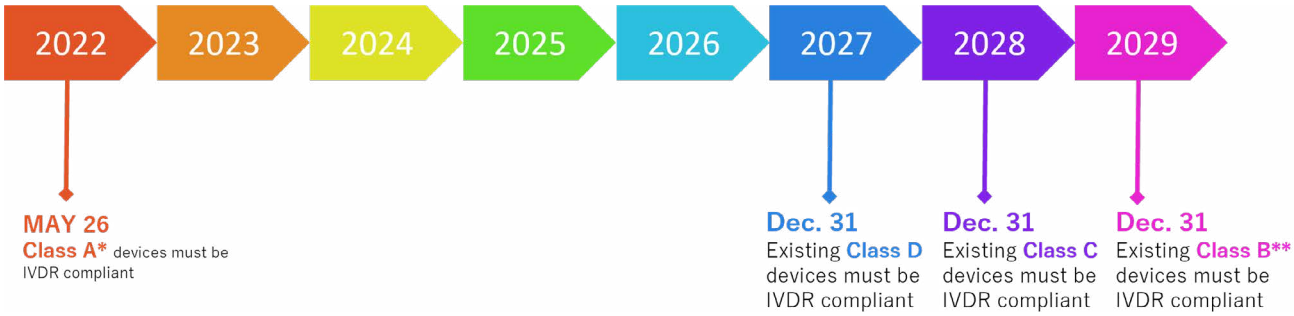
IVDR Transition Timeline

Announced in December 2021



Source: https://ec.Europa.eu/commission/presscorner/detail/en/IP_21_6965

A further postponement proposal in January 2024



* Class A devices without requirements for sterility,

** including class A devices with requirements for sterility

Figure 2. IVDR Transition Timeline

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1 MedTech Europe Survey Report, 8 September 2021.p.6-7.
medtech-europe-survey-report-analysing-the-availability-of-in-vitro-diagnostic-medical-devices-ivds-in-may-2022-when-the-new-eu-ivd-regulation-applies-8-september-2021.pdf (medtecheurope.org)

2 As of 16 February 2024, only 12 Notified Bodies exist.
EUROPA – European Commission – Growth – Regulatory policy - SMCS

3 mdr_in-vitro-proposal.PDF (europa.eu)

In-house devices and IVDR

Another big difference between IVDR and IVD Directive is that IVDR regulates so called "in-house devices" what you know as LDTs or lab-developed tests. IVD medical devices can be manufactured and used within EU health institutions (in-house devices), on a non-industrial scale, to address the specific needs of target patient groups which cannot be met, or cannot be met at the appropriate level of performance, by an equivalent CE-marked device available on the market. In-house devices are exempted from most of the provisions of IVDR, if the health institution fulfills the conditions laid out in IVDR Article 5(5). Here, "health institutions" include not only hospitals but also laboratories and public health institutes which support the health care system and/or address patient needs, but do not treat or care for patients directly.[4] For the details, MDCG guidance[5] is available.

Currently – as transition period – in-house device is possible for health institutions without justifying in their documentation that the target patient group's specific needs cannot be met, or cannot be met at the appropriate level of performance, by an equivalent device available on the market. However, from 31 December 2030 a justifying documentation will be necessary.[6]

"Old" device

It is possible to continue using IVD Directive products already on the market. IVD devices that were placed on the market prior to 26 May 2022 in accordance with IVD Directive and are still on the market or in use after 26 May 2022 are called "old" devices. These "old" devices are in principle not the subject to IVDR requirements. So, these "old" devices can be further used in your laboratory.

However, IVDR provisions which do not directly impact the device, its documentation or the conditions for the placing or making devices available on the market apply also for these "old" devices. Concretely, right and obligations of competent authorities with regard to market surveillance activities (IVDR Article 88 to 95) apply also to "old" devices after 26 May 2022. Also, the reporting and analysis of serious incidents and field safety corrective actions occurring after 26 May 2022 should be also done in accordance with IVDR Article 82 and 84, except for reporting of incidents and market surveillance activities.[7]

4 MDCG 2023-1 Guidance on the health institution exemption under Article 5(5) of Regulation (EU) 2017/745 and Regulation (EU) 2017/746, January 2023, p.3.
mdcg_2023-1_en.pdf (europa.eu)

5 mdcg_2023-1_en.pdf (europa.eu)

Shimadzu IVDR class A solutions for HPLC and LC/MS/MS

High Performance Liquid Chromatography (HPLC) and Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) are used to measure blood concentrations of immunosuppressants, antibiotics, antimycotics, antiepileptics, other TDM, steroids, 25-hydroxy vitamin D, etc. If a Research Use Only (RUO) HPLC or LC-MS/MS is used for diagnostic purposes, it may be converted to in-house device in accordance with Article 5(5) of IVDR.

However, the work required to meet the requirements of Article 5(5) is enormous. Therefore, we recommend the introduction of IVDR class A products for HPLC and LC-MS/MS to reduce the workload. Shimadzu has already launched IVDR Class A devices for HPLC (LC-40 CL) and LC-MS/MS (LCMS-8045/8050/8060/8060NX CL) in 2022. HPLC IVDR class A (Figure 3) is available without MS. Each unit (pump, autosampler, oven, valve, and detector (UV)) is IVDR Class A, so the combination can be customized. For LC-MS/MS, series can be selected according to required sensitivity (Figure 4).

Shimadzu also launched an IVDR Class A device, the CLAM-2040 CL (Figure 5), a fully automated sample preparation module for Shimadzu LC-MS/MS that enables a seamless workflow from laborious pre-treatment to fully automated LC-MS/MS. The CLAM-2040 CL is not only seamless, but also flexible. Depending on the application, you can choose an IVDR class A compliant LC-MS/MS to be combined with the CLAM-2040 CL. The design also allows connection to LIS (Laboratory Information System) and LAS (Laboratory Automation System), enabling a wide range of tests and workflow improvements using LC-MS/MS.

This IVD devices, in combination with commercially available IVD kit, is expected to relieve the user from the enormous amount of work necessary to meet the requirements of Article 5(5) of IVDR. Only the validation by combination is still required.

Detail: https://www.shimadzu.eu/lcms-medical-devices

Application using CLAM: https://www.shimadzu.com/an/products/liquid-chromatograph-mass-spectrometry/lc-ms-option/clam-2040/applications.html#tbaleAnchor_more

6 HYPERLINK EUR-Lex - 52024PC0043 - EN - EUR-Lex (europa.eu)

7 MDCG 2022-8 Regulation (EU) 2017/746 – application of IVDR requirements to 'legacy devices' and to devices placed on the market prior to 26 May 2022 in accordance with Directive 98/79/EC
IVD legacy devices (europa.eu).

Figure 3. Shimadzu HPLC (LC-40 XR/X3 CL)

Figure 4. Shimadzu LC-MS/MS (LCMS-8045/8050/8060/8060NX CL)

Figure 5. Shimadzu fully automated sample preparation module for LCMS (CLAM-2040 CL)

IVD solutions for Immunosuppressants analysis

To face increasing demands on their time and resources, clinical laboratories need easy-to-use solutions that provide fast turnaround times, low cost per sample, and compliance with increasingly stringent IVDR. Shimadzu, in collaboration with Alsachim (a Shimadzu Group company), has developed an optimized high-throughput analytical solution that provides same-day results for therapeutic drug monitoring of immunosuppressive drugs. This is an in vitro diagnostic drug solution that combines HPLC and LC-MS/MS with automated sample preparation and a dedicated IVD kit (DOSIMMUNE™ kit).

Feature

1) Ready-to-use turnkey solution

- Highly reliable – metrological traceability chain
- Easy to set on Liquid Handler by Hamilton STAR CL (IVDR class A)
- Methods and documentation
  Complete documentation including manual with analytical and sample preparation methods, safety data sheets, certificates of analysis, expiry dates, etc.

2) High throughput

One liquid handler and one LC-MS/MS provide results for more than 120 real samples within hours. With two LC-MS/MS units, more than 160 real sample results can be obtained within hours.

2) Stable data

The stable isotope-labeled internal standard (ISTD) in the DOSIMMUNE™ kit can be mixed with the extraction buffer, and mixture can be delivered through the Liquid Handler's automated supply unit. As a result, there is little ISTD area variation for any of the immunosuppressants throughout the three 96-well plates, with a %RSD of less than 5.8 % (n = 288). The method, including automated sample preparation, has been fully validated following international bioanalytical guidelines (ICH M10), including from the Clinical and Laboratory Standards Institute (CLSI C62-A).

Detail: https://www.shimadzu.eu/immunosuppressant-analysis

Related article: https://www.shimadzu-webapp.eu/magazine/issue-2023-01_en/faster-throughput-together/

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