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Article 5(5) of the IVDR

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Contents

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The **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**, known as the **IVDR**, has been applicable since May 2022, but its requirements continue to come into effect following staggered timelines. It was drafted and adopted together with the Medical Devices Regulation (MDR, 2017/745), which has been applicable since 2021. These two regulations aimed to modernise the rules governing medical devices sold on the European market, with the overarching aim of improving patient safety.
Moreover, the IVDR has binding legal force throughout every EU Member State. However, the IVDR includes legal provisions that allow Member States to determine certain matters at the national level, including specific aspects of in-house devices. Therefore, Member States still regulate the local market through national regulations on medical devices, but in the event of a conflict, the IVDR prevails over national legislative acts.

The IVDR impacts clinical laboratories, as it regulates reagents, analysers, diagnostic software, accessories and other IVD medical devices:

- produced and intended by manufacturers to be used for in vitro diagnostic examinations,

Note that these devices should be used by clinical labs according to their intended purpose and instructions for use.

- intended by a health institution to be used for in vitro diagnostic examinations:
    - CE-marked reagents but with a different intended purpose (“off-label use”),
    - utilising research-use only reagents or in-house assembled devices.

Note that in-house devices must demonstrate that the target patient group's specific needs cannot be met by an equivalent device available on the market. Article 5(5)(d).

Off-label or laboratory-developed devices are not equally common across laboratory medicine disciplines. They are rarely found in, for instance, clinical biochemistry, allergology, or transfusiology, but are common in rare-disease genetics or oncogenetics laboratories (where approximately 75% of their device types are developed in-house). Some in-house devices are widely used in a given population, whereas others are tailored to highly specific applications, sometimes designed for a single family or even an individual patient. This trend may stem from limited commercial viability, leading to an "orphan" IVDs scenario.

Article 5(5) exemption

The IVDR permits laboratories to manufacture and use in-house IVDs within their health institutions, subject to several requirements outlined in Article 5(5) of the IVDR.
Clinical laboratories become manufacturers when they make devices from raw materials, combine commercially purchased devices, modify existing devices, or use research-use-only products for clinical purposes. However, sharing laboratory examination protocols between laboratories or referring off-label tests by physicians is not considered manufacturing. Additionally, patient specimens are also not considered IVD medical devices.

Usage of laboratory-developed devices is regulated and limited as follows:

- Devices must be used in-house only
    - For example, even cloud-based IVD software cannot be made available to another healthcare institution (another legal entity) or for patients (lay users)
- No equivalent CE-marked device available (apply from December 31, 2030)
    - Must be supported by a documented justification of unmet clinical needs (lack of CE-marked devices meeting clinical needs)
        - Note that economic motives are not allowable.
        - Examples of specific needs
- CE-marked devices are available only for adult patients, while a paediatric assay is required
- Sensitivity of commercially available assays is not suitable for a specific clinical context
- In-house multiplex assay removes the need for repeated specimen collection compared to separate commercial assays
    - Must be valid (and rechecked) throughout the life cycle of the in-house device

Moreover, some key requirements of Art. 5(5) encompass:
• Implementation of EN ISO 15189 or the applicable national standard for clinical diagnostics laboratories
• Using an appropriate quality management system (QMS), compliant with IVDR requirements for device manufacturers (it is a separate requirement, as EN ISO 15189 might not cover all requirements)
• Reporting obligations – including informing national competent authorities and public declarations
• For Class D (and other classes if mandated by national law) devices, drawing up a set of technical documentation for the device, defined in Article 5(5)(g).

- For example, this requirement is mandatory for Class C devices in Belgium but not in Poland.

• Meeting all relevant general safety and performance requirements (GSPRs) stated in IVDR Annex I as for a CE-marked device
• Obligations for vigilance and implementation of corrective actions

Further guidance and support

To support clinical laboratories and unify understanding of the requirements, the Medical Device Coordination Group issued the MDCG 2023-1 Guidance on the health institution exemption under Article 5(5) of Regulation (EU) 2017/745 and Regulation (EU) 2017/746 in early 2023.
Moreover, national competent authorities often provide further guidance, for instance,

- Belgian FAMPH website
- Irish HPRA website

Moreover, ISO 5649:2024, Medical laboratories — Concepts and specifications for the design, development, implementation, and use of laboratory-developed tests, is available. However, it has not yet been harmonised with the IVDR.

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