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# Consequences of the EU IVDR implementation for medical laboratories

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With the entry into force of the European Regulation (EU) 2017745 ("IVDR") on May 26th 2022, drastic changes have occurred for practically all stakeholders in the field of in vitro diagnostic medical devices (IVD) [1]. Manufacturers are confronted with a new classification concept for their products and, due to the resulting up--classification of products, they have to carry out a significantly more complex conformity assessment procedure for CE marking. Notified bodies face the challenge of meeting the designation criteria and providing the capacity and skills to participate in the conformity assessment procedures. Member State competent authorities often struggle with interpreting market surveillance requirements and implementing their diverse tasks.

Medical laboratories represent stakeholders who, with the IVDR, are directly affected by European legislation in the IVD product sector for the first time. This is because medical laboratories are either health facilities themselves or are part of health facilities to which Article 5 (5) of the IVDR can apply. This section of the IVDR always applies when IVDs from in-house production (so-called "in-house IVDs", borrowed from Anglo-American parlance also known as "Laboratory-Developed Tests-LDT") are manufactured and used within a laboratory without this be placed on the market. Although the IVDR does not apply to these products as a whole, certain conditions must still be met as basic requirements by the relevant health facilities or the health facility laboratories. This includes, among other things, compliance with the applicable general safety and performance requirements according to Annex I of the IVDR and associated documentation, the implementation of an appropriate quality management system, a declaration of conformity of the in-house products, and a justification for the use of the in-house products compared to with test systems that may be commercially available on the EU market.

The European and national medical-scientific societies were initially completely unaware of the integration of these requirements into a legal regulation that constitutes direct law for all EU Member states and of their consequences for medical laboratory diagnostics. Only three to four years after the IVDR came into force that the first publications appeared that made clear the urgent need for action to interpret the IVDR requirements for in-house IVDs and the qualitative and quantitative significance of in-house IVDs for patient diagnostics [2-4].

So, it was just right for the medical-scientific societies and the laboratories concerned that the amending Regulation (EU) 2022/112 introduced new transition periods for certain requirements, e.g. relating to the QM system [5]. These transition periods expire on May 26, 2024 - this year - and on May 26, 2028, respectively.

If the lack of initiative from the laboratory experts with regard to the IVDR requirements can be criticized, this is especially true for the positioning of the official committees of the competent authorities. The European MDCG guideline MDCG 2023-1 "Guidance on the health institution exemption under Article 5(5) of Regulation (EU) 2017/745 and Regulation (EU) 2017/746" was only published five and a half years after the IVDR came into force and after extremely controversial discussions between industry, authority, and laboratory representatives [6].

This guideline, however, clarifies the scope of Article 5 (5). The IVDR does not define a special term for IVDs manufactured in-house, but rather speaks of "products". According to MDCG 2023-1, the definitions in accordance with Article 2, No. 2 of the IVDR apply to these "products". Accordingly, these products include, e.g., reagents, calibrators, control materials, devices, software, and systems which, whether used alone or in combination, are intended for the in vitro examination of specimens derived from the human body. According to MDCG 2023-1, the products addressed under Article 5 (5) IVDR also include so-called "accessories" that meet the definition according to Article 2, No. 4 of the IVDR. The "manufacture and use" of such devices referred to in Article 5 (5) of the IVDR, according to the interpretation of the MDCG Guide, includes various types of combination and modifications of devices with the aim of use in in vitro diagnostic testing. However, the in-house products referred to in Article 5 (5) do not include sample materials and reports, nor standard operating procedures (SOPs) or implementation protocols. However, the latter may be necessary for the use of the "products" and should therefore comply with the applicable requirements set out in Chapter III of Annex I of the IVDR.

In accordance with this, the standard EN ISO 15189:2023, Section 3.9 defines an examination procedure as a "specifically described set of operations used in the performance of an examination... according to a given method". Note 1 to the term further clarifies: "In the IVD medical device industry and in many labo-

ratories that use IVD medical devices, an examination procedure for an analyte in a biological sample is commonly referred to as an analytical method, analytical procedure, or test procedure" [7]. This also confirms that IVDs can have both object-related and procedural dimensions [8]. The view sometimes expressed that the regulation of in-house IVDs would not fall under the responsibility or mandate of the EU, but should be performed by the national medical professions, must therefore be viewed critically [9]. According to Article 168 (7) of the Treaty on the Functioning of the European Union, the individual EU member states are responsible for determining their health policy, as well as for the organization of the health system and medical care [10]. This includes, for example, the implementation of diagnostic procedures and medical laboratory examinations by qualified personnel. But according to Article 168 (4) of the Treaty, the EU has the responsibility and task of contributing to ensuring a high level of health protection through "measures setting high standards of quality and safety for medicinal products and devices for medical use". Of course, this also includes "in-house IVDs".

Apart from MDCG 2023-1, the competent authorities of EU Member States have so far communicated only few guidance on the interpretation and implementation of the IVDR requirements under Article 5 (5). Only the British authority MHRA developed a position paper for Northern Ireland in January 2022 [11]; the Irish Authority HPRA is now following this example with a document presented for consultation in February 2024 [12]. In the latter document, the controversy surrounding the relevance of the EN ISO 15189 standard is taken up again. While MDCG 2023-1 states that a laboratory's sole compliance with the EN ISO 15189 standard does not constitute an appropriate quality management system for the manufacture of in-house IVDs, as this area is not within the scope of EN ISO 15189, the medical laboratory community is of the opinion that EN ISO 15189 is fully sufficient [13]. The Irish draft guidance requires, firstly, laboratory compliance with EN ISO 15189 (with or without accreditation) and secondly, a healthcare facility quality management system covering the manufacture and use of in-house products.

At the European level, it is expected in the future that the problem of the use of so-called "Research Use Only" (RUO) products will be addressed by the Medical Devices Coordination Group as part of a new MDCG edition of the former MEDDEV guideline MEDDEV 2.14/2 rev.1 from 2004 "IVD GUIDANCE: Research Use Only products - A Guide for Manufacturers and Notified Bodies". RUO products are intended for use in medical research and are often a kind of "intermediate station" on the way to a commercially available IVD product. However, they are also used by medical laboratories as a basis for the development and manufacture of in-house IVDs. To date, there is a lack of explanations and examples to clearly distinguish RUO and in-house products from the so-called "products for general laboratory use".

Against the background of not only European but also international intentions to regulate the LDT sector - such as recently through the so-called "Proposed LDT Rule" of the U.S. FDA [14] – ISO standardization efforts for in-house IVD should be considered. The currently developed standard EN ISO 5649 "Medical laboratories - Concepts and specifications for the design, development, implementation, and use of laboratory-developed tests" [15] contains an internationally agreed definition of "laboratory-developed tests" and considers various scenarios for in-house IVD. Among others, the draft standard offers clarification on the question to which extent changes to commercially available test systems lead to in-house IVDs and thus to requirements for these test systems. It remains to be seen whether this standard will provide a useful addition to regulatory guidance in practice.

## Conclusion

European and worldwide efforts to strengthen regulation and standardization for in-house IVDs are significantly increasing. On the one hand, the goal of patient safety and patient protection may require a sensible set of regulations for this area of medical laboratory testing; on the other hand, such regulations must not hinder the innovative capacity and flexibility of medical laboratories with regard to the selection and use of examination procedures in which in-house IVDs play a key factor. This would ultimately torpedo the goal of patient protection.

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## Folker Spitzenberger

Je od roku 2016 profesorem technické univerzity v Lübecku. Pracuje v rámci německé odborné společnosti DGKL v oblasti posuzování a implementace systémů zajišťování kvality klinických laboratoří (QM/QS). Zastupuje DGKL u mezinárodních organizací, jako je WHO a EU v oblasti QM/QS a regulačních záležitostí, podílí se v rámci ISO i na tvorbě norem pro zdravotnické laboratoře. Je členem grémia RKI (Robert Koch Institut) v oblasti zdravotnických prostředků, dále pak i německého zdravotnického dozorového orgánu ZLG, německého akreditačního orgánu DAkkS a německého orgánu tvorby norem (DIN) pro oblast zdravotnických laboratoří.

Časopisu Klinická biochemie a metabolismus poskytl vyzvaný text na aktuální téma implementace IVDR.