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Viewpoint

IVDR and diagnostic application of mass spectrometry in the European Union

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Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices (IVDR) was issued in 2017 and, after a transition period, will apply in the 27 EU states with 447 million citizens from May 2022. It has been published in 24 languages [1]. The IVDR replaces the IVDD (Directive 98/79/EC) and is directly applicable, *i.e.*, it does not have to be transposed into national law first.

For the majority of commercially marketed in vitro diagnostics (IVDs), a certification procedure has been introduced that is carried out by officially supervised, private certification institutes. It represents a significant advance over the previous self-declaration procedure under the IVDD, which does not provide external assessment for most IVDs. However, the procedure differs greatly from the approval procedure used for pharmaceuticals in the EU. The effort for manufacturers, with regard to documentation of production, post-market surveillance and other requirements, increases significantly. This also applies to commercially offered mass spectrometry (MS) products such as kits, but also to complete systems that are declared as IVDs.

The Treaty on European Union [2] is an international treaty between the member states. Article 168 in Title XIV (Public Health) states that Union action shall respect the responsibilities of the Member States for the definition of their health policy and for the organization and delivery of health services and medical care. Union action shall complement national policies. The IVDR, is therefore in principle, not entitled to regulate medical practice in clinical laboratories of the member states. High standards for the quality and safety of medical devices, however, is explicitly mentioned as a goal in Article 168.

The IVDR lays down rules concerning placing on the market, making available on the market or putting into service *in vitro* diagnostic medical devices and accessories for such devices (Art. 1). The IVDR does *not* regulate the *operation* of IVDs or the oversight of their operation, which is done at the member state level.

Article 2 of the IVDR defines an *in vitro* diagnostic medical device as "*. . . any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body. . ..*". A *kit* is defined as a set of components that are packaged together and intended to be used to perform a specific *in vitro* diagnostic examination, or a part thereof. The term *system* is not defined.

According to Article 1, the IVDR does not apply to products for general laboratory use, unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for *in vitro* diagnostic examination (Article 1).

The IVDR does not use the term *Laboratory Developed Test (LDT)*, nor does it use *in-house test*. Only the term *devices manufactured and used only within health institutions* is used. The word *device* is reasonably understood to mean that the IVDR is intended to address only tangible elements. The only non-physical item mentioned is software. Procedures and protocols cannot be understood as *devices*. The regulation of processes and complex workflows of measurement procedures performed in a medical laboratory would be in conflict with Article 168. These complex procedures have to be regulated as part of medical practice on a national level.

Art. 5, para. 5 of the IVDR is relevant for in vitro diagnostic devices manufactured within a health institution. If few conditions are met, the IVDR as a whole does not apply to *in vitro* diagnostic medical devices manufactured within a health institution, with the exception of Annex 1 (general safety and performance requirements), which also applies to devices manufactured in-house.

Annex 1 comprises 239 individual points. Among other things, a risk management plan is required for each device. In addition, metrological traceability must be demonstrated for calibrators [3]. A large part of the requirements in Annex 1 are not of relevance to specialized laboratories, e.g., the requirements for devices for patient self-testing.

Among the conditions that must be met in order for the IVDR not to apply to IVDs manufactured in-house, is that the laboratory: (i) has an appropriate quality management system (citing in particular the ISO 15189 [4] standard), (ii) monitor the experience gained from clinical use, and (iii) make a public declaration about the device (particularly regarding conformity with Annex I). The devices must not be produced on an industrial scale.

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An essential questionable condition is formulated in Art. 5, para. 5, clause (d); according to this, the health institution must justify in its 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. This "*industry privilege*" is a central problem for highly specialized laboratories. Primarily, the unsuitability of a third-party product must be proven, and only secondarily the suitability and performance of their own. It seems that the potentially *superior* performance of an in-house device compared to a commercial product is not per se a valid justification for its use under this clause. The physicians' freedom to choose methods is thereby called into question – that is, their freedom to select the most appropriate diagnostic tool for their patients, also with regard to the economic efficiency and available resources of a national health care system. Here, there is a risk of deep intervention in national health systems.

If a self-developed, complex, mass spectrometric measurement procedure is configured and declared as a *kit,* according to the IVD definition, by the health care institution, the "industry privilege" is likely to be in effect: as soon as a commercial kit-product for the same intended use is marketed in one of the 27 EU Member States, probably the unsuitability of this product would have to be conclusively demonstrated or their own method would potentially have to be discontinued.

Unless declared as a kit, complex mass spectrometric measurement procedures and protocols probably cannot be considered a *device*. According to a medical-diagnostic protocol, IVD (especially calibrators) are used together with products for general laboratory use (e.g., a generic mass spectrometer) in the sense of medical professional practice. As another example of complex measurement procedures in the clinical laboratory, the classic microscopic differential blood count - reading out a percentage distribution of different cell lines in a diagnostic blood sample – can hardly be called a *device*. However, *devices* with the same intended use are commercially available.

An obvious shortcoming of the IVDR is that "*industrial scale*" is not defined, which makes the standard ambiguous. Furthermore, the term "*equivalent*" is not specified in Art. 5 [5] d: are methods equivalent if simply the same quantity is determined in the same material, e.g., is an immunoassay for ETG measurement in urine equivalent to an MS method for the same purpose? Or is equivalence related to analytical figures of merit too?

A guidance document on in-house devices is currently being developed by a sub-group of the Medical Devices Coordination Group (MDCG) of the European Commission; it is expected to be available from Q2 or Q3 of 2021. It is hoped that the above ambiguities will be clarified.

The IVDR addresses the putting into service of *in vitro* diagnostic medical devices from in-house manufacturing (Article 5, para 4 and Article 1). This area, however, is not overseen by a European authority. In fact, the surveillance of compliance with the IVDR is a matter for the competent authorities of the member states, which interpret Article 5 of the IVDR. There can be potentially significant differences between member states in this regard.

The possible impact of the IVDR implementation on measurement procedures developed or implemented in diagnostic laboratories on a non-industrial scale is currently interpreted heterogeneously [5–8]. This particularly concerns the question of whether or when such measurement procedures are to be regarded as *devices* within the meaning of the IVDR and whether the IVDR consequently regulates such measurement procedures as a whole.

Declaration of Competing Interest

The author declares that he has no competing financial interests or personal relationships that could have appeared to influence the viewpoints reported in this paper.

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