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Letter to the Editor

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In-house diagnostic devices under the EU IVDR and unwanted side-effects of intentional transparency

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To the Editor,

The European Commission Medical Device Coordination Group (MDCG) releases regularly guidelines on the interpretation and implementation of clauses of the EU Regulation 2017/746 on *in vitro* diagnostic medical devices (IVDR) [1]. The guidelines are typically developed in a consultative process between national competent authorities (CA), and take or take not into account opinions of invited observer stakeholders. These guidelines start with a general disclaimer that they cannot be regarded as reflecting an official position of the European Commission, that views expressed are not legally binding and that only the Court of Justice of the European Union can give binding interpretations of Union law. However, being an accepted guideline, they may stand in court as a reference to diligent good practice.

Recently, MDCG-2023-1 [2], a guideline pertaining to the interpretation of art 5(5) of the IVDR [1] for implementation of laboratory developed tests (LDTs) for in-house use

was published. In this particular guideline, the words “shall, should and harmonized” occur 6, 38, and 3 times, respectively. At least, the use of the verb “shall” risks to be at odds with the above disclaimer. So does reference to harmonization in the absence of harmonized standards.

As a counterweight to the opinions expressed in MDCG-2023-1, we want to use this letter to refer to opinions expressed in our recent publication on the implementation of LDTs under the IVDR [3]. While the IVDR has the laudable purpose of improving patient safety and cleaning up the market of substandard devices, we argue that unwanted side-effects may be a breakdown of laboratory services, if administrative overload of both laboratories and CAs and duplication of accreditation standards are not avoided. With respect to the latter, we are of the opinion that ISO 15189, explicitly named in IVDR art 5(5), suffices as a tool for IVDR-compliant implementation of LDTs, provided adequate interpretation.

The IVDR is concerned with the manufacture, placing on the market and putting into use of physical and software devices (IVDR art 2). It is concerned with the smooth functioning of the market and not with their medical use [3, 4]. In accordance with the principle of proportionality of the Union Treaty [5], the IVDR should not go beyond what is necessary to achieve its objectives (IVDR preamble 101). This being said, we refer to the introductory sentence of art 5(5) of the IVDR. With respect to laboratory developed tests restricted to in-house use, the article explicitly excludes requirements embedded in other articles, except “relevant” safety and performance requirements set out in Annex I. “Relevant” allows for judgment calls, which elsewhere in the article 5(5)f(iii) have to be documented with a reasoned justification. Laboratories are acutely aware of the need for such modifications [6] and should be allowed to restrict the implementation to “relevant” elements of the IVDR [3]. As a reminder, the IVDR cannot infringe on 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 (treaty on the functioning of the union, art 168 para 7) [5].

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We want to expand on two issues with respect to MDCG-2023-1. ISO 15189 states (art 1) that international requirements may apply to specific topics of the standard. This implies that activities accredited under ISO 15189 conform with the IVDR. Now, the authors of the MDCG-2023-1 are of the opinion that the manufacturing process of laboratory developed devices is not in the scope of the ISO 15189, presumably by lack of itemized concordance with other chapters of the IVDR or Annex I of the IVDR. This opens the door for the introduction of as yet unnamed additional requirements and harmonizing explicit standards, contrary to the restrictions put forward in article 5(5) on the scope of the IVDR with respect to in-house devices tests. The ISO 15189 (versions: 2012 [7]; 2022 [8], resp.) in the chapters on facilities, laboratory equipment, reagents and consumables (5.2 and 5.3; 6.3 and 6.4), examination processes (5.5; 7.3) and profusely elsewhere provides ample opportunity to implement manufacturing requirements of the IVDR.

We also want to draw attention to risk management requirements. In our paper [3] we argued that the complexity of medical testing foregoes strict one-size-fits-all recipes. Both the ISO 15189 and the IVDR allow for a risk-based interpretation of requirements. Indeed, the IVDR recognizes this in its use of “relevant, where applicable or appropriate”. The IVDR Annex I, Chapter I, art (1) takes a precautionary approach to safety referring not only to patient safety, but also to safety of users and bystanders, and elsewhere not only to effects on diagnosis and clinical care, but also on effects of the physical, radiation and chemical implications during manufacture and use of the devices. ISO 15189 refers to management of risk to patient safety under 4.14.6 (15189:2012) and 5.6, 8.5 (15189:2022) and diffusely in both standards by referring to fitness for intended clinical use in chapters on method validation, reference ranges and reporting, and refers to risk for users and bystanders under 5.2 (15189:2012) or 6.3 (15189:2022) on accommodation and environmental conditions. ISO 15189 refers to ISO 15190 [9] with respect to safety issues.

The “precautionary” approach of the IVDR is not one of “an abundance of caution” but is balanced with preservation of the benefit-risk ratio of the device (Annex I, Chapter 1, art. 2). The health institution has to justify adaptations that turn legacy devices into LDTs. Allowed changes comprise extensions of the intended use or changes to the design and use of the device to improve performance or safety [6]. In many instances, it will suffice to single out the aspects that require additional validation, and to demonstrate that the device became safer at an unchanged diagnostic intent, or that the device become diagnostically more performant at an unchanged level of risk.

The MDCG-2023-1 states that compliance with EN ISO 15189 alone does not constitute an appropriate QMS for the manufacture of in-house IVDs. We want to point to the distinction between certifiable ISO competence standards (ISO 15189) and technical standards, such as ISO 22367 on risk management [10]. The latter is not a standard for accreditation. It provides recipes to choose from wisely. Competence means that you trust the laboratory professionals to make wise choices.

In conclusion, provisions ensuring transparency of conformity assessment and surveillance (IVDR preamble 4) has translated into an elaborate system of checks and balances. An abundance of parties and hand-overs results in calls for sprawling interpretations and guidelines. So also, for laboratory developed in-house devices [2]. However, risk-aversion of laboratories and CAs results in trading in litigation risk for the freedom to choose the best solutions in complex environments. An abundance of quality assurance comes with opportunity costs for the health care system. The net result may be detrimental to patient care [3]. While the IVDR aims at the smooth functioning of the internal market, and thus article 5(5) protects the investment of economic operators, by restricting the use of laboratory developed tests to in-house use in the absence of suitable devices on the market, conversely the investment of laboratories involved in innovative translational research is less well protected.

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