Opinion Paper

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Urgent call to the European Commission to simplify and contextualize IVDR Article 5.5 for tailored and precision diagnostics

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Abstract: The European Commission (EC) started targeted evaluations and public consultations regarding the EU IVDR 2017/746 to assess its effectiveness, efficiency, relevance, and EU-added value. The goal is to identify implementation challenges and unintended consequences, experienced by either IVD-manufacturers that put CE-IVDs on the EU market or by medical laboratories that establish and operate in-house-IVDs (IH-IVDs) in their healthcare institution (network). Based on stakeholder feedback the EC aims to be informed about potential regulatory revisions by late 2025. As IH-IVDs, used in different modes, have a vital role in the EU healthcare system, the authors make the statement that Article 5.5 of the IVDR should be systemically amended, removing conditions (a) and (d) through (i) for in-house tests, while retaining conditions (b) and (c). Having the prime objectives of the IVDR in mind, i.e. patient safety and clinical utility, this opinion paper urges the EC to revise IVDR Article 5.5 to prevent disservices to patients and caregivers by taking into account available quality management infrastructure in ISO 15189:2022 accredited medical laboratories and guaranteed professionality of registered laboratory specialists, both already monitored at the level of the EU member states. By abandoning unnecessary, non-valuable requirements from Article 5.5 overregulation is prevented and the sustainability of important specialty and orphan tests, essential for patients with rare diseases, is guaranteed.

Keywords: European Commission; IVDR Article 5.5; disproportionate regulation; IH-IVDs; precision diagnostics

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Introduction: IVDR Article 5.5 does patients a disservice

Article 5.5 of the IVDR (EU 2017/746) regulates IVDs, which are (1) *de novo* created or (2) used for a test purpose other than the intended purpose in the clinical care pathway as mentioned in the Instructions for Use, or (3) assembled from CE-marked kits and other reagents, e.g. research-use-only (RUO-) kits or reagents, or developed from scratch with basic chemical and biological substances or (4) modified CE-IVDs because of

suboptimal performance of the commercial tests, causing demonstrable patient harm (Table 1). In the terminology of medical laboratories, such IVDs are called in-house IVDs (IH-IVDs).

The IVDR regulates the EU-market access of commercial medical tests which should be safe and effective, whereas lab developed tests or tests in complex analytical workflows established in healthcare institutions are considered an exemption. Yet, there is an Article 5.5 in the IVDR which imposes stringent obligations on medical laboratories that use essential IH-IVDs in different modes for specific intended uses in which commercial tests do not foresee, either by not being available, by not being evaluated for specific test purposes, or by being available but not fulfilling clinical needs [1]. In the IVD-directive (IVDD 98/79 EC) dating from 1998, IH-IVDs were not regulated. They were just mentioned as not being regulated at all.

The IVDR allows IH-IVDs to be used for healthcare provided all provisions set in Article 5.5.a through 5.5.i are met. Yet, the rules in several of Article 5.5 subheadings are detrimental to the development and use of IH-IVD.

For example, EU 2017/746 Article 5.5.a: "*the devices are not transferred to another legal entity*". Consequently, within the EU all IH-IVDs are available exclusively at the single laboratory sites where they have been originally devised from. This would require all patient samples in need of the respective analysis to travel to the respective IH-IVD-providing laboratories resulting in a serious disservice for patients in need of specialized diagnostic devices and also in a burden for the healthcare system.

Table 1: Different modes to establish in-house IVDs (IH-IVDs) according to IVDR 2017/746 nomenclature or Lab Developed Tests (LDTs) according to ISO 5649: 2024 terminology [11].

In-house IVD test (IH-IVD) or lab-developed-test (LDT): a test or examination which is designed, developed, manufatures (or modified) and used within a single laboratory or laboratory network to carry out testing on samples, where the results are intended to assist in clinical diagnosis or be used in making decisions concerning clinical management
Mode 1: "First principle" LDTs developed from first principles (*de novo*): applies when a laboratory is responsible for the design and production of the examination
Mode 2: LDTs developed or modified from a published or any other source, e.g. from scientific literature, from the specifications of an LDT manufactured by another laboratory
Mode 3: LDTs developed as assembly or combination of commercially authorized IVD medical devices and other, non-IVD products to a novel system for *in vitro* diagnostic purposes
Mode 4: LDTs used for a purpose other than the intended purpose assigned by the commercial manufacturer, including significant changes of the IVD, etc.

To fully implement Article 5.5.a,

- an EU-wide logistics net must be established for medical specimen transport.
- appropriate intermediate storage facilities and pick-up must be warranted for batch-wise shipping.
- a dedicated IT infrastructure is necessary for tracking and administration of the EU-wide sample traffic.
- biomaterial and data safety are to be regulated for the specimen traffic (a patient safety issue).
- delays in testing must be avoided, as long turn-around-times impede timely diagnostics (a patient safety issue).
- preanalytical requirements and compromised biomolecular quality of specimens leading to questionable testing results need defining (a patient safety issue).

While we appreciate that Article 5. 5.a. aims preventing secondary "grey markets" of IH-IVDs being distributed across the EU to the disadvantage of diagnostics manufacturers, its implementation will create major disbalances in the "availability map" of highly specialized IVDs mostly provided by science-driven academic laboratories. Obviously, stakeholders need to agree to solutions. For example, IH-IVDs could be distributed between specialized academic laboratories on a non-commercial basis provided equivalence and exchangeability of test results of distributed IH-IVD is warranted. Furthermore, single (i.e. academic) laboratories developing IH-IVDs as one of their academic core tasks may not be disadvantaged compared to commercial laboratory chains acting as single legal entities (with EU-wide representations).

EU 2017/746 Article 5.5.d asks laboratories to *justify* in their documentation that the performance requirements of the IH-IVDs in use in their target patient groups cannot be met by similar products available on the market or cannot be met at the indicated level of performance. This might lead to the bizarre situation that laboratories develop a new test and publish it scientifically. After a certain time, this test may also be offered by industrial manufacturers. From that point onwards the laboratory must prove the superiority of its own test in case of doubt or use the commercially available test. This makes the development of IH-IVDs totally unattractive because developing tests is a time-consuming and costly process. Also, laboratories could simply wait until IVD-manufacturers bring these tests on the EU-market. The recent COVID crisis showed us impressively where this would have led to: there would have been no early PCR detections or later lollypop self-tests. It is obvious that Article 5.5.d must be deleted without replacement.

Such initiatives to regulate IH-IVDs are not limited to Europe. For example, the US FDA started an initiative in 2015 to get oversight about IH-IVDs, named Lab Developed Tests (LDTs), but, following consolidated lawsuits from the

American Clinical Laboratory Association (ACLA) and the Association for Molecular Pathology (AMP), FDA's LDT Rule was struck down by a USA District Court on March 31, 2025. The court determined that FDA's attempt to regulate LDTs as medical devices under the Federal Food, Drug and Cosmetic Act (FDCA) was not supported by the statute's language, structure and was arbitrary, capricious and an abuse of discretion. The court especially emphasized that *LDTs are primarily professional* services *provided by clinical laboratories that include the total testing process rather than tangible products* like medical devices or commercial tests in a kit. The ruling highlighted that Congress had already established a distinct regulatory framework for clinical laboratories under the Clinical Laboratory Improvement Amendments (CLIA) since 1988, and that FDA's attempt to regulate LDTs through the FDCA was not consistent with this established CLIA framework. The court vacated FDA's final rule, effectively halting the planned phased implementation of FDA oversight for LDTs. FDA decided not to appeal the ruling and not to pursue further legal action.

Article 5.5 of the EU IVDR requires medical laboratories, which use IH-IVDs, to prepare additional documentation such as clinical evidence, proportionate to the intended use and risk class and to have a quality management system in place which fulfills the requirements of the globally accepted standard EN ISO 15189:2022. It does not specify how this fulfillment of requirements can be proven to third parties. Documenting clinical evidence – encompassing scientific validity, analytical and clinical performance – is the responsibility of the healthcare institution that develops IH-IVDs and makes the performance claims. Because EN ISO 15189:2022 is an accreditation standard which is restricted to medical laboratories, an obvious way to do that would be to get accredited. This is not required by the IVDR but is left to EU-member states to regulate, which is expected to lead to 27 different solutions. Furthermore, because medical laboratories have spearheads and/or deliver (supra)regional or (inter)national activities e.g. as a reference laboratory, samples are increasingly exchanged between member states, so different national rules can create obstacles to cross border healthcare. In addition, some accreditation bodies are not happy with medical laboratory accreditation and do not want to consider IVDR-requirements in their audits and audit reports. So, accreditation according to EN ISO 15189 is not practiced uniformly throughout Europe and cannot support the implementation of IVDR sufficiently [2]. National competent authorities are entrusted with market surveillance and vigilance of IVDR in their national context and therefore have to check for compliance of medical laboratories with IVDR and Article 5.5 with periodic inspections based on spot checking of medical laboratories.

As a consequence, medical laboratories in Europe are in the complex situation that they are required to be checked at two different and independent levels, i.e. by their accreditation body and their national authority. This is disproportionate and burdensome and as the inspections and audits are carried out by two different institutions with different interpretations of requirements, this leads to conflicting non-conformities which cannot be resolved. In addition, there is ample room for varied interpretation of IVDR Annex I requirements and their application to IH-IVDs. Therefore, medical laboratories may try to get rid of their IH-IVDs and hence in some clinical pathways (e.g. orphan diseases, metabolic diseases …) the level of patient care will deteriorate.

Recognizing the professionality of registered laboratory specialists employed in accredited medical laboratories

Validation of a medical test is defined as a process to assess analytical and clinical performance of the test compared to predefined performance specifications that should be met to implement a *fit-for-clinical-purpose* test. The European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) working group on Test Evaluation has developed a cyclical Test Evaluation Framework [3] and a toolbox to guide lab professionals on *how* the five key elements of medical test evaluation – i.e. analytical performance, clinical performance, clinical effectiveness, cost-effectiveness and the broader impact-interact and affect patient management and outcome [3–8]. The fulfillment of clinical needs or gaps in clinical care pathways is *de facto* a key goal of the IVDR as regulatory requirements expect medical tests to be safe and effective, i.e. *fit-for-clinical-purpose* in the specific target populations and settings.

EN ISO 15189:2022 is the international standard for medical laboratories in Europe, and holding and maintaining the accreditation status proves that the medical laboratory has the competence and the capacity to verify and to validate laboratory tests within its accredited scope. So, Article 5.5 should be revised to require accreditation of medical laboratories, which want to establish, use and report IH-IVDs. National authorities should be obliged to accept accreditation certificates as proof that the medical laboratory is competent to devise, validate and use IH-IVDs. Accreditation certificates should be sufficient to guarantee the quality of IH-IVD services and should eliminate the

burden of being evaluated by both accreditation bodies and national competent authorities, creating potentially conflicting inspections results. It establishes an equal playing field for medical laboratories in Europe and could further their role as a source of diagnostic innovation.

The EU-commission should consult with European Co-operation for Accreditation (EA) as described in EU-regulation 2008/765 on accreditation to make sure that the level of accreditation audits is homogenous throughout Europe and the interpretation of requirements is comparable between accreditation bodies. This should be periodically monitored.

In Article 5.6 of the IVDR the European Commission is permitted to adopt implementing acts on the interpretation and practical application of Annex I, in case of divergent interpretations and practical implementation. EFLM and other interested parties could support the Commission to adopt such an implementing act to clarify open issues with General Safety and Performance Requirements and IH-IVDs [3–8].

There is an additional aspect, which has to be dealt with as well: EN ISO 15189 does not include requirements for developing medical tests, whereas MDCG-2023-1 [9] mentions EN ISO 13485:2021 as an appropriate standard for the production of test kits. Yet, this standard is applicable for IVD-manufacturers, which are producing IVDs for commercial use in the EU-market. At first sight the ISO 15189 standard´s requirements may appear not to be fully applicable to medical laboratories establishing IH-IVDs for tailored solutions in multistep workflows and precision care pathways, only for internal use and not putting them on the market. To solve this ambiguity, the EFLM Committee on European Regulatory Affairs (EFLM C-ERA) and the EFLM Working Group Accreditation and ISO/CEN Standards published a joint opinion paper noting that ISO 15189 is a sufficient instrument to guarantee high-quality manufacture of IH-IVDs for *in-house* use conform requirements of the European *In-Vitro*-Diagnostics Regulation [10].

Medical laboratories in the EU that are not yet accredited to ISO 15189:2022 may use ISO 5649:2024 as a guidance document [11] (note this is not a normative reference) as it holds requirements for assuring quality, safety, performance and documentation of LDTs as per their intended use for the diagnosis, prognosis, monitoring, prevention or treatment of medical conditions. ISO 5649:2024 outlines the general principles and assessment criteria by which an LDT should be designed, developed, characterized, manufactured, validated (analytically and clinically) and monitored for internal use by medical laboratories.

As a service to patients with rare diseases, it could be helpful to specifically register orphan IH-IVDs in a European database. This could support the identification of medical laboratories offering specialty, low-volume tests on a European level and non-commercial basis, and could also alleviate the problem of orphan diagnostics. Furthermore, such a register could help laboratories to exchange validation data on rare/orphan IH-IVDs and facilitate the dissemination of established IH-IVDs.

The path forward: revising Article 5.5 to proportionate legislation

We conclude that IH-IVDs in this era of P5 medicine (i.e. Predictive, Preventive, Personalized, with Participation of the patient and considering Psychosocial aspects) have a vital role in the healthcare system and deliver essential diagnostic testing for a broad spectrum of unmet needs, from analyzing measurands of interest in special body fluids and making modifications to overcome the limitations of suboptimal commercial tests, to tests for rare or niche diseases, emerging pathogens, precision medicine such as precision oncology, and also during pandemics. Indeed, with the expansion of personalized medicine and the growing demand to provide specialty applications, the “footprint” of IH-IVDs will further widen in laboratory medicine. Hence, IH-IVDs in the hands of qualified, registered European laboratory specialists (either medical doctors or non-medical doctors) who are accountable for the total testing processes in ISO 15189:2022 accredited laboratories should in essence be trusted and should be proportionately regulated (intended purpose and risk class based) to enable informed clinical decision support in specific settings to prevent patient harm [12–15]. Therefore Article 5.5 of the IVDR should be amended systemically, removing conditions (a) and (d) through (i) for in-house tests, while retaining conditions (b) and (c). Criterion 5.5.a limits the capacity of academic laboratories to share expertise and methods for e.g. rare disorders and precision diagnostics, which are often not covered by industrial devices. The industry privilege in criterion 5.5.d limits the capacity and incentive of laboratory specialists to establish rational solutions for clinical unmet needs in specific healthcare settings. Its abolition will support continued innovation.

Failure to amend Article 5.5 along the above lines will increase healthcare costs, jeopardize the ability to design “personalized” laboratory tests, discriminate patients with metabolic and/or rare diseases, stop innovation and withhold essential and/or tailored diagnostic services to caregivers.

It is prime time to reverse the multiple unintended consequences of IVDR Article 5.5 and to scrutinize its requirements, taking into account the real-world context of medical laboratories in healthcare institutions, staffed with

diagnostic laboratory specialists performing different modes of IH-IVDs under risk-averse quality management systems in accredited laboratories for up to three decades [10, 12, 13], with qualifications in managing measurement and diagnostic uncertainties. Secondly, academic institutions in medical analytics should be strengthened and supported by the European Commission as centers of excellence and drivers of innovation. Thirdly, EU-citizens and patients should be protected and repositioned in the center of diagnostic care in this era of precision medicine.

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