Review

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ISO 15189 is a sufficient instrument to guarantee high-quality manufacture of laboratory developed tests for in-house-use conform requirements of the European *In-Vitro*-Diagnostics Regulation

Joint opinion of task force on European regulatory affairs and working group accreditation and ISO/CEN standards of the European Federation of Clinical Chemistry and Laboratory Medicine

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Abstract: The EU *In-Vitro* Diagnostic Device Regulation (IVDR) aims for transparent risk-and purpose-based validation of diagnostic devices, traceability of results to uniquely identified devices, and post-market surveillance. The IVDR regulates design, manufacture and putting into use of devices, but not medical services using these devices. In the absence of suitable commercial devices, the laboratory can resort to laboratory-developed tests (LDT) for in-house use. Documentary obligations (IVDR Art 5.5), the performance and safety specifications of ANNEX I, and development and manufacture under an ISO 15189-equivalent quality system apply. LDTs serve specific clinical needs, often for low

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volume niche applications, or correspond to the translational phase of new tests and treatments, often extremely relevant for patient care. As some commercial tests may disappear with the IVDR roll-out, many will require urgent LDT replacement. The workload will also depend on which modifications to commercial tests turns them into an LDT, and on how national legislators and competent authorities (CA) will handle new competences and responsibilities. We discuss appropriate interpretation of ISO 15189 to cover IVDR requirements. Selected cases illustrate LDT implementation covering medical needs with commensurate management of risk emanating from intended use and/or design of devices. Unintended collateral damage of the IVDR comprises loss of non-profitable niche applications, increases of costs and wasted resources, and migration of innovative research to more cost-efficient environments. Taking into account local specifics, the legislative framework should reduce the burden on and associated opportunity costs for the health care system, by making diligent use of existing frameworks.

Keywords: European Regulation 2017/746 on *In-Vitro*-Diagnostic Devices; ISO 15189:2012; laboratory-developed tests for in-house use; method validation.

Abbreviations: AB, accrediting body; BRCA1/2, breast cancer genes 1 and 2; CA, competent authority; CAPA, corrective and preventive actions; CDx, companion diagnostics; CGP, comprehensive genomic profile; CRGA, clinically relevant genomic alterations; EFLM, European Federation of Clinical Chemistry and Laboratory Medicine; EU, European Union; EEA, European economic area; EMA, European Medicines Agency; FMEA, failure-mode effects analysis; GA, genomic alterations; GDPR, General Data Protection Regulation; HI, health institution; HRD, homologous recombination deficiency; HRR, homologous recombination repair; iQC, internal quality control; ISO, International Organization for Standardization; IVDD, *In-Vitro* Diagnostic Device Directive; IVDR, *In-Vitro* Diagnostic Device Regulation; LDT, laboratory-developed test; MDCG, Medical Device Coordination Group; MSI, micro satellite instability; MU, measurement uncertainty; NB, notified body; NGS, next generation sequencing; NTRK, neurotrophic tyrosine receptor kinase; PARPi, poly (ADP-ribose) polymerase inhibitors; PRRC, person responsible for regulatory compliance; PT, proficiency testing; RiliBÄk, Richtlinie der Bundesärztekammer zur Qualitätssicherung Laboratoriums medizinischer Untersuchungen; RUO, research use only; SOP, standard operating procedure; TMB, tumor mutational burden; UDI, unique device identifier; VAF, variant allele frequency.

1 Introduction

In 1991, the weekly L'Événement du jeudi reported that the French Centre National de Transfusion Sanguine in 1984–1985 knowingly distributed HIV-and Hepatitis C-contaminated products to hemophiliacs [1]. Recently, in the Poly Implant Prothèse breast prostheses scandal patients were given implants manufactured with tainted industrial grade silicone [2]. In both cases patients across national borders fell victim.

An analysis executed in the courts and in the public opinion revealed: fraudulent self-declaration of compliance with safety requirements, insufficiencies in the certification of product properties, lack of traceability in the manufacturing process and in the use of the products, lack of transparency of decisions about purchasing products and underestimation of risks associated with these decisions.

To improve patient safety the European legislator replaced existing directives by two new regulations on Medical Devices (MD) [3] and *In-Vitro* Diagnostics (IVD) [4]. Both follow an almost identical structure concerning intended use, economic operators, supervisory authorities and technical and administrative addenda to transparently secure safety. The Medical Device Coordination Group (MDCG) registers the consultation between the European legislator, national competent authorities and stakeholders about legislation and guidelines. A multilayered net of European and national competent authorities (CA), notified bodies (NB), European reference labs (ERL) and Expert Committees is involved in registration and certification of production facilities and devices. Economic operators have to assign a person responsible for regulatory compliance (PRRC). Unique device identification (UDI) codes are introduced and a European data repository (EUDAMED) [5] keeps track of economic actors and of devices and lots along the whole manufacturing and distribution chain. Synopses of products performance characteristics and of post market surveillance are available for the public. Medical devices used in patients are traceable up to the lot-number.

The IVDR [4] Art 16.1 allows the in-house use by health institutions (HI) of modified commercial devices or of their own devices. Art 5.5 details conditional and documentary requirements and restrictions and refers to ANNEX I for safety and performance requirements. In what follows, we will demonstrate that ISO-15189 [6] compliance, explicitly referred to in the IVDR, suffices to fulfill IVDR requirements for laboratory-developed tests (LDTs). We argue for the continued availability of low volume high value testing and warn against impeding the development of novel tests addressing clinical needs.

1.1 Timelines and impact

Entry into force of the IVDR [4] was planned for May 26 2022. The European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) commented on uncertainty of continued availability of commercial legacy devices and on the impact of implementing the IVDR for LDTs [7]. The European Community legislator published an amending act [8] extending the timelines (Figure 1). The introduction of the REACH regulation [9] may force redesign of devices with respect to accepted reagents and additives, potentially affecting the performance of the devices. This will also add to the workload. The MDCG follows up the roll-out of the elements of the new regulatory framework and their capacity to manage the transition of IVDD legacy devices to avoid market disruptions and a collapse of diagnostic services [10]. Despite a will across the sector to seek workable solutions, the obstacles remain formidable, and the potential solutions so far proposed remain more a matter of aspirations than of clear pathways [11].

In typical clinical laboratories, over 95% of routine laboratory results are produced using IVDD and/or IVDR-conform devices, while the remainder is produced by LDTs for which there is no commercial alternative, or commercial devices only fulfill the laboratories requirements after extension of the intended use or by modification of the design, or commercial devices cannot be run on available platforms [12, 13].

For large volume commodity tests such as routine chemistry and hematology tests, the LDTs will correspond to a small fraction of the bulk revenue generated by the laboratory. Other specialized tests may have a market share that is too small to interest economic actors. These tests will entirely depend on LDTs. In rare or orphan diseases, the majority of tests make use of "for research use only" (RUO) components. Even when these tests are often concentrated in a few specialized laboratories, relatively small volumes and costly development might become prohibitively expensive. By the same token, we expect many IVDD legacy commercial IVDs with limited economic interest to disappear from the market, forcing the laboratories to develop LDT alternatives. Absent the numbers involved, the dates set forward in Figure 1 dictates the timeframe for their discontinuation. LDTs add to the workload for the HIs and CAs.

In summary, the laboratory has to bring about 50% of its test portfolio responsible for less than 5% of reported results into IVDR compliance [12]. Per the timelines summarized in Figure 1, this implies demonstrating absence of equivalent commercial devices that meet the target group's needs at the appropriate level of performance (IVDR 5 (5) d). The HI has to validate the LDT according to

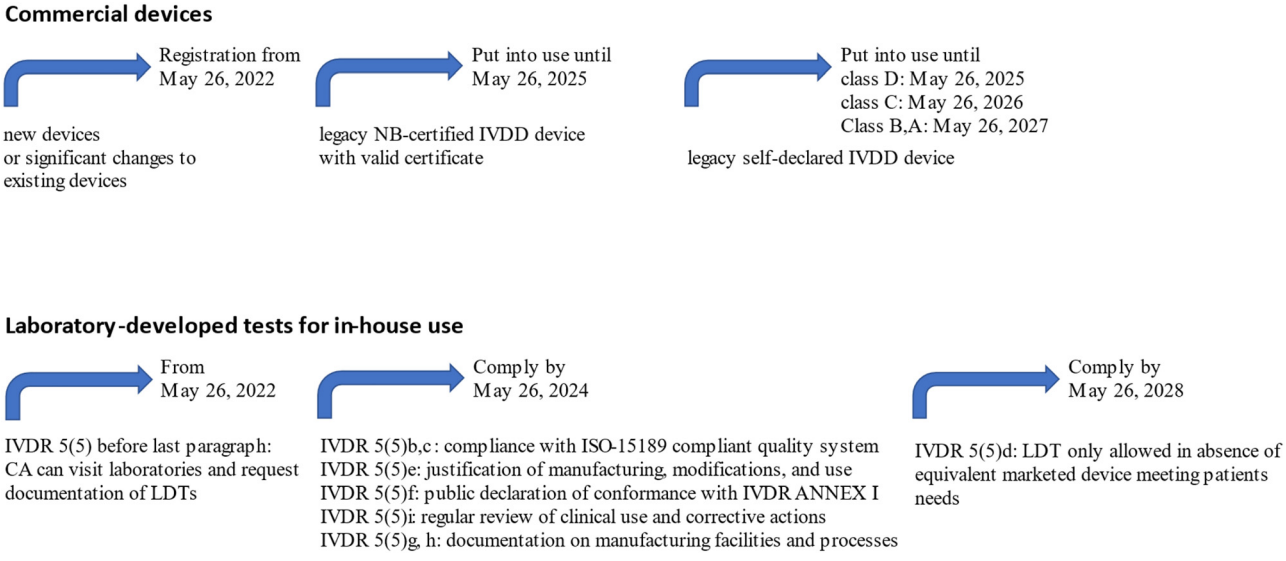

Figure 1: Protracted timeline for IVDR-compliant implementation of in-house laboratory-developed tests (LDTs). This is a non-authoritative abridged interpretation of the amending EU regulation 2022/112 [8]. As of the date of submission of our paper, the revised timelines are as indicated in the Figure. Commercial devices put into use can be used beyond the times indicated in the Figure, as long as they are within the applicable expiration period. The extended timeline for commercial devices results in the extension for the IVDR 5 (5) d requirement on the absence of marketed equivalent devices. With respect to LDTs: IVDR 5 (5) g applies to class D devices, but member states can extend this at will to other classes.

IVDR ANNEX I, and to fulfill extra documentary requirements (IVDR5 (5)). For the highest risk class (IVDR ANNEX VIII), the HI has to draw up a document sufficiently detailed for its CA to be able to understand the manufacturing process and to ascertain whether the general requirements of IVDR ANNEX I are met. The devices cannot be manufactured on an industrial scale, and cannot be transferred to other legal entities (IVDR 5 (5) a). For all other LDTs the HI provides a justification for their manufacture upon request by the CA. The CA can inspect the manufacturing activities at the HI.

2 On regulatory compliance

IVDR regulates the putting into use of diagnostic devices, not the professional use of the devices. The latter is the subject of licensing and professional oversight, while IVDR-related inspection and auditing activities are limited to the former.

The IVDR implicitly recognizes the ISO 15189 as an equivalent standard (IVDR 5 (5) c). Many but not all countries mandate it for some or all medical laboratory activities [14].

National accrediting bodies (AB) assess laboratories according to ISO-15189 and deliver accreditation certificates for the competence to perform a scope of diagnostic procedures. The accredited scope refers to types of analytical competences and to the medical field of application [15]. While in some countries, accreditation is mandatory for the operation of the medical laboratory [14], generally, ABs have no direct policing authority. By contrast, national CA have a broader legal span. They can request information from HIs about in-house LDTs, can do unannounced inspections, and have punitive power.

Guiding principles of both the EU 2017/746 IVDR and the ISO 15189 are system thinking and risk-based measures to ascertain fitness for the intended purpose. Table 1 summarizes concordance between the IVDR 5 (5) articles and ISO 15189 clauses. The IVDR focuses on the production and putting into service of devices that reliably produce usable results. Besides this, the ISO 15189 standard also focuses on the competence to decide on auxiliary procedures and to engage in consultative services with the users.

Several authors reflected on the suitability of these frameworks for in-house LDTs. They focus on interrelated questions: (i) is the IVDR sufficiently precise about requirements [12, 13], (ii) how to implement the IVDR within an ISO 15189 framework [13, 16–18] (iii) also taking into account the national organization of medical services [19], and most importantly (iv) how to safeguard the intricacies of the medical diagnostic service that laboratories provide [20, 21] against unwanted effects of the IVDR [22].

Table 1: Requirements for LDTs: the ISO 15189 mapped on the EU IVDR.

ISO 15189:2012	EU 2017/746 IVDR 5 (5)
Primacy of local regulations (introduction, 1)	Refers to ISO 15189 (5.5 c)
Conditions requiring “validation” (5.5.1.3 a-d)	Laboratory developed tests (5.5)
Fit-for intended use (5.5.1.3)	Intended purpose (5.5 d)
Preferred procedures (5.5.1.1)	Scientific validity (ANNEX I)
Requirements for intended use fulfilled (5.5.1.3)	Clinical performance (ANNEX I 9.1 a)
Analytical performance (5.5.1.3)	Analytical performance (ANNEX I 9.1 b)
Risk management (4.14.6) & safety (5.2.1)	Safety (5.5 f iii, ANNEX I chp I)
Management review (4.15.2 a)	Surveillance (5.5 I, ANNEX I 9.2)
Equipment (5.3.1), reagents, consumables (5.3.2)	Manufacturing of devices (5.5 g, h)
Register validation-file (5.5.1.2)	Draw-up summary statements (5.5 e, f)
Information for users (5.4.2)	Transparency to users (5.5 f)

The Table summarizes equivalent clauses of ISO 15189 and IVDR requirements. We follow here the analysis as also published elsewhere [16] based on the ISO15189:2012 version. During the final stage of this document a new 2022 version has been published [74]. In essence it covers the same elements as the 2012 version, albeit in a different order. It is even more focused on clinical intent of methods and benefit/risk ratio for patients, and uses risk management as its method for validation. Thus, it remains fully in line with the IVDR. The 2012 version remains in force for a transition period of 3 years. We intend to publish a detailed updated table at the documents page of the EFLM WG ISO/A [75].

In what follows, we will argue with respect to LDTs that the ISO 15189 standard is fully suited for validation and assurance of IVDR performance and safety requirements, and does not stand in the way for fulfilling the documentary requirements of the IVDR. Commensurate implementation of the IVDR can limit the operational and financial burden for the health care system.

3 Use of ISO 15189-conform method validations to demonstrate compliance with IVDR requirements on device performance and safety

The MDCG developed guidance on the requirements of ANNEX I [23, 24]. The guidance focuses on intended use, scientific validity, analytical and clinical performance, and

design with patient safety as its main focus. While in first instance intended for IVD manufacturers, LDTs also have to comply unabridged with the requirements of ANNEX I. The MDCG produced guidance to the interpretation of Article 5 (5) for LDTs [25].

3.1 Preliminaries

3.1.1 The intended use

A clinical care pathway describes the processes to manage a specific medical condition in a specific target group of patients [26]. The medical test purpose relates to how the test information will be used to improve clinical management of patients. Test purpose includes: diagnosis. prognosis, monitoring, early detection, screening, risk classification, treatment selection and surveillance after treatment. The test role describes how the test is used for a specific clinical purpose or how it is used to optimize a specific care pathway. The test can be positioned either as a replacement test, a triage test or an add-on test in the care pathway.

The IVDR uses a more restricted definition of intended use. It refers to what is measured in which sample, how it is measured, in which target population, for which diagnostic purpose without explicit reference to clinical care pathways. It forms the basis for defining requirements on performance and safety from the viewpoint of the “intended use” of the device. Table 2 provides guidance on questions to evaluate when describing the intended use of the diagnostic device.

The intended use is the standard against which to weigh whether a suitable device can be found on the market for a given application, and whether any HI-specific peculiarities about the use of such devices are significant to qualify as off-label use turning it into an LDT. For both off-label devices and self-developed devices the intended use drives safety considerations and risk-analysis and the required clinical and analytical performance.

3.1.2 Absence of device with the appropriate level of performance on the market

LDTs address a clinical or operational need not met by available devices on the market. In Figure 2 we propose an applicable decision tree.

The proposed scheme starts with a market exploration. With the deferred timelines mentioned in Section 1.1, Figure 1, the laboratory only has to demonstrate the absence of an equivalent device on the market from May 26, 2028. Meanwhile IVDs put onto the market under the old IVD directive are phased out. In the absence of a marketed device, or marketed devices not fulfilling the appropriate level of performance, we can resort to the LDT. When we decide to modify a marketed device, we have to justify the modification and its use (IVDR 5 (5) d-e). This requirement came into force from May 26 2022, although the documentation will only to be available from May 26 2024 [8].

Existing devices are weighted at our performance criteria. These include intended use, safety considerations, clinical and analytical performance and operational requirements. Operational requirements can be, but are not limited to following examples: turn-around time required by the patient care programs serviced, availability in the laboratory of technical platforms, and guaranteed supply.

Table 2: Defining the intended use of the device in the clinical care pathway.

Clinical question/clinical scenario
– Screening, monitoring, diagnosis or aid to diagnosis, prognosis, prediction, companion diagnostic, …
– Physiological or pathological state, congenital physical or mental impairments, predisposition to a medical condition or a disease, safety and compatibility with potential transplant recipients, prediction of treatment response or reactions, selecting and monitoring therapeutic measures (companion tests refer to International Non-proprietary Name of Therapeutic), …
– Position of the device in HI-specific care pathways: availability and use of other diagnostic facilities, patient turn-over, …
Measurand(s)
– In matrix (ces)
– Analytical method (automated or not)
– Measurement type (nominal, ordinal, interval, ratio)
– Commutability to certified (in matrix) reference materials or the methods used in the clinical studies from which decision limits are derived
Target population and prevalence of condition(s) to be discerned
Appropriate level of performance: this is inherently related to …
– Clinical performance: e. g. which clinical performance is needed and which level of diagnostic uncertainty at defined values is acceptable
– Analytical performance: e. g. does the analytical performance at relevant decision limits guarantee the required level of clinical performance
– Equivalence of performance claims of devices available on the market

For the IVDR the intended use defines the device in terms of the intended measurement, the site of sampling, the users, and the intended clinical use for a defined target population. Relevant definitions with reference to clinical care pathway context can be found elsewhere [26].

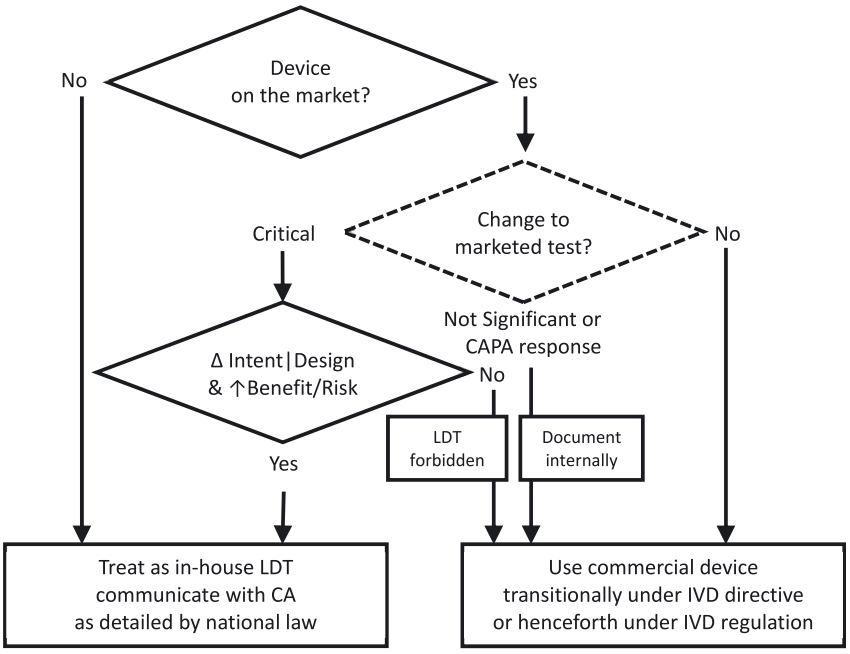

Figure 2: Weighing the LDT with respect to the IVDR 5 (5) d non-equivalence requirement. The flowchart summarizes decisions to be made when deciding about whether an application has to be treated as an LDT. The diamond in dashed lines corresponds to MDCG 2022-6 for legacy devices [27]. In the absence of equivalent guidance, we apply it here also to LDTs. Decisions ending in the "not-significant" path have to be documented internally. Although the obligation for documentation of absence of an equivalent commercial device is postponed for existing LDTs till 2028, this test precedes the diamond in dashed lines, because in the event of a modification of an IVDD-registered test after May 26 2022 the latter date of entering into force of the IVDR still applies to new LDTs.

If a change to a marketed device is required, then we have to evaluate whether such change is critical. A critical change will turn it into an LDT, requiring proper validation. By contrast a non-significant change does not have to be handled as a relevant deviation of the original device. We adopt here guidance on the significance of changes with respect to transitional provisions for commercial legacy devices [27]. Table 3 summarizes elements to consider in the risk-analysis to decide on the criticality of changes to devices. When evaluated as critical these elements will then have to be addressed while validating the LDT for use. Contrary to medical devices, diagnostic devices are seldomly used as a stand-alone element in diagnosis and or treatment selection. We propose to use Table 3 not as a prescriptive tool, but as a checklist allowing for educated choices. Under Section 4 we discuss examples of evaluation of criticality and commensurate actions. The analysis is independent from the risk classification according to ANNEX VIII. The role of tests and their position in clinical care pathways and the risk for and consequences of misdiagnosis or missed diagnosis has to be taken into consideration when evaluating criticality of changes.

Table 3: Evaluating criticality of changes in existing methods.

A. Extension or change to the intended purpose
– New user or patient population
– Change of clinical use (anatomical site/sample matrix)
B. Change in design or performance specification
– Requires further clinical or usability data
– New risks/existing risks require redesign of control measures
– Change to operating principles/control mechanisms
C. Change in software/interpretation of results
– Operating system/database structure/channels of interoperability
– User interface
– Algorithms/diagnostic features
D. Change in materials and manufacturing
– Change of equipment components/reagents/calibrators
– Ingredient or material from new supplier does not meet existing specification
– Change in shelf life

The table guides us through initial steps of the risk analysis. It corresponds to the decision step "Change to marketed test" in Figure 2. We list here elements that may or may not carry a hitherto unrecognized risk. A failure mode effect analysis will guide us on the appropriate validation experiment to perform to exclude risk, or to decide on mitigating measures. The residual risk will determine which path we then follow in the decision tree in Figure 2.

3.1.3 Risk classification according to ANNEX VIII

Having defined the intended use, we can assign the applicable risk class (Table 4). This risk classification is more granular than that of the old directive that it replaces, and defines documentary requirements dictated by the IVDR art.5.5.

3.2 Method validation: fulfillment of the requirements of ANNEX I

LDTs have to comply with the requirements of ANNEX I. The method validation will recognizably address: scientific validity (the measurand is related to the diagnostic purpose), analytical performance (much as in the old directive), clinical performance, and safety. A risk-based analysis has to give evidence of the benefits and safety. The legislator took a "precautionary" approach to safety, naming multiple hazards for patients, users and bystanders. Published summary statements assure transparency for the end-user.

The MDCG developed guidance intended for IVD manufacturers on the implementation of ANNEX I [27–29]. Guidance is not legally binding, but it provides a backdrop against which to judge due diligence and state-of-the-art implementation. Guidance cannot cover the wide range of clinical applications, analytical methods, and HI-specific implementations of care pathways. With respect to the latter, clinical and operational requirements can set HI-specific performance criteria. The EFLM WG on test evaluation established a comprehensive framework for test evaluation that encompasses five key elements [26]. The EFLM Test Evaluation framework goes beyond the IVDR requirements as besides scientific validity, analytical and clinical performance, also clinical effectiveness, cost-effectiveness and the broader impact of medical tests are considered. A test is fit-for-clinical-purpose when it produces actionable results fulfilling the needs of the specific clinical care pathway. Needs not met by existing devices correspond to the IVDR absence of an equivalent device criterion. Although not explicitly cited as such by the IVDR, actionable results, clinical effectiveness and cost efficiency correspond to clinical benefit in the IVDR benefit-risk ratio evaluation. The EFLM TF on Performance Specifications in Laboratory Medicine also proposed a specific framework for setting analytical and clinical performance specifications for the purpose of method validation and quality assurance [30]. The EFLM WG-ISO/A also proposed guidance for the distinction between method validation and verification according to the ISO 15189 [31]. A corollary of the advent of the IVDR is that from now on a broad segment of compliant commercial tests are validated in a transparent manner, and henceforth method verification by the laboratory suffices for these tests. For modified tests, a risk analysis can identify the elements that need additional validation, without a need for a repeat validation of unaffected aspects. In what follows, we strictly adhere to the IVDR requirements. However, the above-mentioned frameworks provide useful guidance.

Table 4: Summary of risk classification according to the intended use.

Rule 1: transmissible disease in blood derived products, tissues, transmissible life-threatening agents	class D
Rule 2: Immunological compatibility of blood products, transplants	class D
Rule 3: mostly all other tests, inclusive POCT	class C
Rule 4: self-testing	class C
but: pregnancy, fertility, cholesterol	class B
glucose, erythrocytes, leucocytes, bacteria in urine	class B
Rule 5: general accessories and consumables	class A
Rule 6: unclassified by the above	class B
Rule 7: controls without assigned value	class A

The Table is an abridged summary of addendum VIII of the IVDR. The classification is based on the combined criticality for individual and public health care. Risk is determined not only by the nature of the disease but also by the risk for mistreatment due to the risk of faulty results. The MDCG Guidance on Classification Rules for *In-Vitro* Diagnostic Medical Devices under Regulation (EU) 2017/746 provides extra information [76].

3.2.1 Scientific validity

The scientific validity refers to evidence for the association of the measurand with the clinical condition or physiologic state on which the test provides information, and to state-of-the art performance characteristics [32]. The intended use of the device (see Table 2) can be used to draft a literature research question attesting to the above. For novel applications guidelines on carrying out validating experiments are available [26, 33]. Obviously, for these novel applications the input comes from translational research by laboratory specialists. That research will also validate the clinical utility, and for innovative research almost invariably will have been published in peer-reviewed literature.

3.2.2 Risk-based validation: process and system-thinking

To ascertain patient safety, the IVDR-compliant device validation best starts from risk analysis. It results in an appropriate control and safety program and identification of residual issues. For residual risks, a rationale for not covering them has to be produced. Table 5 can guide us in

Table 5: Risk-analysis approach to the requirements of the ANNEX I.

Cover complete process:
– Brain to brain concept: Advice on which test to choose/test-request/ results/reporting/advice on interpretation and further actions=from pre-pre-and pre-analytical over analytical to post-and post-post analytical
– Analytical process: from set-up equipment, preparation/conditioning of consumables, sample preparation, running the experiments to output of results
Risk management:
– Distinguish between risk, failure, harm
– Distinguish between avoidable and unavoidable failure, acceptable and unacceptable harm
– Inventory of signals to identify failure (timely=preferably before any harm is done)
– Prefer primary prevention (no failure will occur) over secondary prevention (action triggered by failure)
– Plan mitigation of harm
Cover critical elements in validation/quality assurance/safety plan (for the others argue why they do not need to be covered)
Manufacturing aspects for in-house use:
– Selection of suppliers and products?
– What do you know about degradation pathways, and appropriate detection of degradation/failure?
– Is the stability of equipment and consumables timely covered by quality control procedures/scheduled maintenance?

The Table can be used to guide us through the risk analysis. The proposed list covers the complete diagnostic cycle, focuses on the quality of risk detection and harm mitigation, and retraces critical infrastructure.

the risk-analysis exercise. Processes involved in intended clinical care pathways are analyzed from start to finish [34, 35]. A value chain or a fishbone analysis, naming all consecutive components with their interdependences forms the basis of a failure-mode effects analysis (FMEA). Effects of conceivable failures are weighed for risk of occurrence and time to detection, harm done, and opportunities to prevent or remedy harm [34].

The IVDR explicitly focuses on manufacturing of physical or software devices. The ISO 15189 covers these aspects in sections on equipment and consumables (ISO 15189:2012 5.3) and information technology (ISO 15189:2012 5.10). The laboratory produces test results. Results are sampled for patient-based control procedures and/or the test process is evaluated by internal quality control procedures (see below), and thus tests the quality of the underlying devices. The authors are of the opinion that additional standards such as ISO 13485 [36] are not required for LDT implementation by ISO 15189 accredited laboratories.

3.2.3 Analytical and clinical performance

Adherence to ANNEX I amounts to the clinical and analytical validation and safety of the devices. We discuss clinical and analytical performance under one handle, as these are interdependent and determine the fitness for clinical purpose of the tests and have downstream consequences for patients, *inter alia* the clinical and cost effectiveness (the latter not strictly demanded by the IVDR). For inspection purposes, it is wise to identify both aspects clearly in the technical documentation.

ANNEX I (Art 9 (1) a) lists elements for validation of quantitative measurements. We have to select the appropriate elements relevant to the fitness for purpose: applicability of the method; selectivity and interferences; linearity and intercept; matrix variation and matrix effects; final calibration procedure; trueness and appropriate reference values or reference materials or reference method; spiking/recovery and interference experiments; measurement uncertainty, precision and limits of detection, determination, and quantitation; response sensitivity; ruggedness [37]. In the validation plan, we argue why certain elements do not need to be evaluated, and relevant elements have to be translated into technical requirements. We recommend to document these choices by a generic approach to classes of applications. For class D devices EC common specifications apply [38].

For quantitative results (ratio and interval measurements), the performance qualifications typically translate to traceability and measurement uncertainty. With respect to traceability and as this directly relates to clinical performance, the commutability with the methods used to define clinical decision limits (see Table 2) has to be evaluated and where this becomes an issue, we have to consider revision of decision limits and or reference values or application of correction of results for known relative bias. Measurement uncertainty (MU) refers to random error [39]. Main sources of random error are the measurement system by itself, calibrations and the uncertainty on values assigned to the laboratories working calibrators, and when applicable, uncertainty on corrections for known bias. A reasoned evaluation has to be presented for bias that cannot be unequivocally attributed or cannot be reasonably estimated. For tests with good clinical performance, MU is well within allowable performance specifications, and does not excessively contribute to diagnostic uncertainty. Having set performance qualifications and having determined MU, we can also set allowable lot-to-lot variability [40]. For tests with inherent poor biological resolution, reduction of the noise usually has only a borderline effect on their clinical performance. In other cases, reduction of MU extends the measurement range at the lower end, allowing more sensitive detection of low levels of the measurand. Also, MU forms the basis for setting up quality assurance strategies. The narrower the MU, the smaller the relative bias that can be detected with the least number of repeat measurements

of the control materials. As this also applies to clinical reference change intervals, it obviously also relates to clinical performance.

To the extent that semi-quantitative (ordinal) and qualitative (nominal) results are derived from an underlying quantitative measurement, and these are available, the above approach for quantitative measurements can be applied. Both quantitative and qualitative results found in clinical samples can be compared to diagnoses, assigned by preferably "golden standard" methods, or by "equivalent" methods. Obviously, diagnostic concordance relates both to analytical accuracy and to clinical utility and longitudinal and transmural commutability.

The analytical and clinical performance also have to be appreciated with respect to the personnel performing the test. Especially, near-patient testing and self-testing involves persons not trained in laboratory medicine, and this can affect both the reliability of results and patient safety. Near-patient testing is performed for non-stable metabolites (e. g. blood gases) or in care pathways where one wants to trigger immediate actions according to the results found (e. g. glucose, coagulation). Often modern systems have self-diagnostics combined with software indicating the type of a possible malfunction. Nonetheless, not recognizing faulty results can trigger life-threatening faulty treatments (e. g. potassium infusions, insulin dosing, lack of or excess anti-coagulants). These examples help to illustrate the importance of a systematic process-oriented approach, taking into account the analytical and pathophysiologic literacy of the operators of the devices.

3.2.4 Formulating the conclusions of the validation study: the safety plan

Where appropriate, the above analysis has to result in actions to reduce risks and to prevent harm. These include but may not be limited to: process care, instructions for and training of users, parametrizing the internal quality system, continuous post-implementation surveillance.

Process care is a tool for primary prevention, reducing the occurrence and costs of failures and thus optimizing the benefit/cost ratio. It can be directly projected on the above risk analysis. It encompasses: mapping value adding steps across care pathways, eliminating redundant steps, making critical steps appropriately robust, and making communication part of the process, standardizing procedures and planning control procedures and maintenance [41, 42].

LDTs require standard operating procedures (SOP) for manufacturing the device and for performing the test, instructions on sampling and sample handling, information about indications for test requests, laboratory manual for requesters [43] and thoughtful presentation of results which can be correctly interpreted by medical personnel and patients alike. Significant harm to patients is most likely to occur at the pre- and post-analytical phase of the process [44]. Sentinel events have to be pre-defined, and without delay registered, investigated and appropriately handled. Treating physicians have a pivotal role in recognizing unlikely results, and in exerting due caution when prescribing potentially dangerous treatments. Hence, transparent communication between laboratory and care takers about use of tests and interpretation of results and actual and residual risks has to be planned and followed up to reduce the occurrence of adverse events.

The internal quality control (iQC) procedures ensure stability of the analytical system and they need to be parametrized to that end. Typically, this means determining the number of observations needed to detect a gradual or a sudden deviation exceeding an allowable relative bias given the estimated MU, and defining the number of observations for which the range of results will be used to detect deterioration of said MU. iQC is a diagnostic tool to assess the performance of your analytical processes. With frequent sampling to detect seldom events, it is prone to false positive alarms. The selection of rules has to minimize false alarms using a sparce harmonized set of detection rules and action escalation cascades [45]. Appropriate escalation schemes have to ensure that released results are trustworthy, but also that unwarranted delays in release of results are avoided as to do not cause harm by delaying needed additional diagnostic or therapeutic interventions [46]. These measures relate to the risks associated with devices, but extend beyond the IVDR scope.

For commercial tests that have been modified, appropriate proficiency testing (PT) may be available. To the extent that the materials are commutable over different applications, they provide information on the accuracy of reported results, and hence on the clinical performance with respect to the correct interpretation of results. When available PT-schemes are not appropriate, or for LDTs developed from scratch for a niche application for which no PT-scheme is available, the ISO 15189 provides alternative approaches (ISO 15189:2012 5.6.3.2). Typically, these schemes are tested too infrequent to serve as a control mechanism. Yet, relevant differences with results from the peer group have to be investigated and require documentation of causes and eventual actions. Illustration of commutability also provides confidence in the use of results from different laboratories in trans-mural patient trajectories. Participation in these schemes can be part of the post-implementation surveillance plan (see point 3.4, hereafter).

3.3 Drawing up summaries for public information and inspection purposes

For all LDTs, the HI makes publicly available the legal identity of the HI, details identifying the device, a self-declaration of conformity with ANNEX I and when applicable a statement on unmet requirements with a reasoned justification. A centralized national depository of these data can assist laboratories in search of a HI for outsourcing tests that they do not perform in-house. The laboratory manual for requesters preferably refers to this depository. Otherwise, the laboratory manual can serve as a tool for dissemination of the requested information.

For class D LDTs, the laboratory draws up documentation that allows the CA to understand the manufacturing facilities and manufacturing process, the intended purpose of the device, fulfillment of safety and performance requirements. In an ISO 15189 compliant quality system this documentation exists and is readily accessible.

3.4 Surveillance plan – maintenance

Bookkeeping of manufacturing and use of devices is required [25]. Throughout the full life cycle of a device, changes in conditions surrounding the use of the devices, in the manufacturing processes, and in safety measures shall be evaluated and documented, and performance data shall be regularly reviewed and updated, and unwanted events and corresponding corrective and preventive actions (CAPA) shall be documented. It forms the basis of continuous vigilance.

4 Case studies: ISO 15189 conform implementation of IVDR requirements

Laboratory procedures do not only comprise single devices used for a corresponding measurement, but often comprise complex multi-step schemes such as microscopic examinations, tuned spectroscopy, etc. requiring skilled laboratorians making on the spot judgement calls [22]. This professional activity goes beyond the IVDR regulation on devices.

About half of the different test methods in a laboratory might be classified as LDTs [12, 13]. Efforts to bring them into IVDR compliance may not be commensurate with the test volume, as many of these LDTs apply to low-volume tests. The workload will become unmanageable for laboratories and CAs, unless non-critical changes to commercial tests are allowed (Figure 2, Table 3) without turning them into an LDT, and national legislators do not extend regulatory oversight by CAs to non-class-D LDT devices. Given the wide divergent scope of possible LDTs, all-encompassing strict guidance is nearly impossible and would stifle future innovations. In what follows, we will demonstrate at the hand of a selection of cases, how diligent interpretation of the IVDR can reduce the workload. ISO15189 provides an excellent framework for implementation of tests conform IVDR requirements. Our professional competence is required for appropriate interpretations of IVDR requirements.

4.1 Changes in matrix for well-established methods

The laboratory offers comprehensive metabolic [47] and hematologic [48] panels for the detection and diagnosis of ailments, and for follow-up of treatments. These high-volume applications are vested in a long clinical tradition, as exemplified by their occurrence in multiple clinical guidelines and medicine textbooks. Thus, additional clinical data are not required. The manufacturer validated some of these tests for blood serum as the matrix. Serum is a typical sufficient matrix for laboratories receiving samples from remote locations. Other laboratories receive most of their samples from hospital wards and work with heparinized plasma to shorten the turn-around-time, and the time-to-diagnosis and-treatment, operational requirements of the care pathway. The change of matrix is a critical element that however can be validated in isolation. Samples for both matrices are drawn from subjects covering the whole pathophysiologic range of results (corresponding to required clinical data), and results for the plasma matrix are correlated with the serum comparator. The experiment is covered by the HI ethical committee, and the laboratory has proof of informed consent by the subjects. An appropriate statistical analysis is performed (analytical performance), resulting in appropriate review of reference ranges (clinical performance). Appropriateness is evaluated by comparison with published intra-and inter-individual biological variation, and by participation in PT schemes. This is a wide-spread policy across HIs, and reliance on published and shared information is also acceptable.

A properly executed ISO 15189 audit will cover all of these elements. Strictly speaking, the implemented method qualifies as an LDT, but the ISO-15189 conform validation should suffice as an argument validating that (Figure 2,

Table 3) the change was not critical and that additional administrative burdens are not warranted.

4.2 Use of tests outside their standard context

A surgeon seeks advice about the nature of a liquid oozing from a drain. The laboratory reacts to this clinical question by measuring proteins, lipids, metabolites, and organ-specific enzymes, released nucleic acids and a cytologic examination of cells. The clinical question does not turn this into a class D issue. With respect to the quantitative tests, a literature search of case reports shows that these non-validated tests can and have been used to answer the surgeon's question [49]. This confirms the scientific validity and clinical performance. A full-flagged analytical validation is not commensurate with the intended use, and hence not appropriate. In concordance with published literature the responses that will lead to a conclusion are clearly off-scale. Thus, analytical performance does not require that the exact same tests as in the publications are used and does not require additional proof of traceability, linearity, or measurement uncertainty. These arguments constitute our validation of the tests, and "the non-validated status in ISO 15189 parlance" will be properly communicated with the users.

Changes to the stated intent or the matrix for which the tests are certified turns them into an LDT. The laboratory offers this "off-label" use for occasional compassionate use. In the laboratory manual and on the reports, we define the test stating the matrix and it's off-label unvalidated nature. We comment that the interpretation relies on a conjecture of test results and needs to be confirmed by the clinical presentation and where possible by appropriate specialized imaging or other examinations. As a class C test, we have not to report this to the CA. In case of inspection by the CA we refer to the laboratory manual and the Laboratory Information System (LIS) report definitions of the tests, which informs the user about the drawbacks cited in the above summary validation.

With respect to the cytologic evaluation, this is essentially an inspection and not a measurement activity [50], and thus, falls beyond IVDR device classification rules and performance criteria. With respect to detection and characterization of released nucleic acids within alternative body fluids (pleural, ascitic, plasma, etc.), when the tissue cannot be analyzed, this requires caution, in the absence of internationally recognized standards in terms of volume of samples, type of molecular assays, cut-offs for reporting genetic variants, actionability of identified targets. It requires skilled laboratory specialists who communicate their expert evidence with the clinician in a deliberation dialogue [22], and this professional service is also beyond the scope of the IVDR.

4.3 Precision diagnostics

The standard of care for solid [51, 52], myelo-[53, 54] and lymphoproliferative [55, 56] neoplasms involves selection of treatment options guided by clinically relevant genomic alterations (CRGA), and this has resulted in spectacular improvements in clinical outcomes. Genetic testing focuses on expression of germline and somatic genetic variants. Two very different diagnostic strategies prevail. Targeted detection of genetic "hotspot" mutations known to be pathogenic using allele-specific methods or next generation sequencing (NGS). Secondly, comprehensive genomic profiling (CGP) can be used to scan for genomic alterations (GA) across many cancer-related genes. Both strategies require their own metrics and pipelines, yet both need to comply with the IVDR.

With the rapid development and availability of massively parallel analytics technologies, all tumors will be increasingly screened for a broad variety of actionable genes without prior knowledge of the clinical utility of the diagnostic results. Specifically, the number of druggable targets and candidate therapeutic compounds rapidly expands for personalized treatment regimens. Hence, we need to acknowledge that the number of targets to be tested and potentially acted upon by the oncologists, is highly dynamic and thus requires an expandable scope definition. The respective diagnostic tests are under continuous development and evaluation in research-oriented laboratories and (international) networks actively advancing translational medical approaches outside the realms of classical "intended-use" applications. In addition, highly selective diagnostic question will determine the use of analytical platforms, growing databases and IT tools within dynamic workflows. So, continuous changes in diagnostic intent and in method design and use defines these in-house diagnostic tests and consequently implies the absence of timely available commercialized alternatives.

Performance qualification and post-market surveillance follow from the "dynamic" appreciation of "clinical performance" in the networks. Continued maintenance of competence referring to this increasing body of knowledge is in line with ISO 15189 accreditation criteria. Sample processing, analysis, and predictive analysis delineated from molecular information involving bioinformatics pipelines and artificial intelligence engines are often spread over

multiple participating HIs. Contractual arrangements stipulate the exchange of services, and external quality assessment and assurance. The interpretation of the individual case results from an integrative multi-disciplinary deliberation dialogue involving laboratorians, pathologists and oncologists [57].

Similarly, laboratories use custom gene panels and bioinformatics pipelines for genetic testing of rare diseases, often adapted to the specific medical condition in question in accordance with national or international recommendations. Moreover, there is no systematic harmonization of pipelines for exome sequencing (regularly improved supplier kits) and genome sequencing, and differences between tools are more related to the number of genes covered by the assay than the complete utility in clinical settings.

Mutatis mutandis, as modern medicine moves towards more individualized health care, much of the above also will apply to other fields in the forefront of modern diagnostics, like metabolomics and proteomics [58], that also involves customized platforms, and shared dynamically growing databases and analytical pipelines.

In some countries, laboratories already are required to seek accreditation of their competence for these activities under ISO 15189 [14]. “Flexible” reference to a “broad application scope” and to “ad-hoc builds of analytical infrastructure” is managed compliant with ISO 1589 [15]. A “fixed” static preconceived planning-implementation-cycle is replaced by “dynamic” well-documented “project management” with “continuous surveillance” and registration and correction (CAPA) of undesirable outcomes. Only by applying the same approach “creatively” to IVDR requirements, laboratories will be able to keep serving patient’s needs, simultaneously safeguarding against substandard practices and to retain spearhead translational research within the EEA.

4.4 Companion diagnostics

Precision diagnostics applies to selection of treatment options to optimize expected outcomes and/or minimize undesirable side effects. They can be used both at the time of initial diagnosis, or for follow up in the course of the treatment. Often tissue is collected for future analysis in the course of the disease, and/or deposited in biobanks. When these applications are a prerequisite to qualify for a particular clinical treatment, they are defined as companion diagnostics (CDx). For in-house CDx, the validation of performance is covered by registration of the clinical study protocol and audits by clinical study sponsors [59, 60]. HI often finetune CDx to fit into the HI workflows [61]. The European Medicines Agency (EMA) discusses CDx aspects on a regular basis, foremost analytical and diagnostic prowess [62]. MDCG guidance acknowledges the use of in-house LDTs in medicinal clinical studies [24]. The existing safeguards should suffice to ascertain safety and thoroughness of clinical studies, without impeding access of study sponsors to cooperating HIs.

4.5 Software

The IVDR has broadened the definition of an IVD to include also software, either as an integral part of a device, or as a stand-alone application. In summary [63], the IVDR applies when a programmed algorithm provides information relating to the intended medical purposes of the IVDR (art 2.2) and the input is substantially dependent on IVD’s. The component with highest IVD risk class dictates the ultimate risk class. When the software is developed or sold as a package limited to storage, archival, communication and simple search functionality it does not classify as medical device [28]. This would apply to the LIS, and the middleware used to communicate with the analyzers.

Standard parametrizations of software, like reference limits, conversion of units, but also simple calculated parameters, such as creatinine clearance or metabolite over creatinine ratios are part of the diagnostic interphase that laboratory professionals establish for supporting diagnostic stewardship. Not implementing them should be interpreted as not safeguarding the intended use of the underlying devices. The above simple algorithms should not classify as LDTs in their own right, not warranting additional administrative burdens. Algorithms creating new diagnostic information should be carefully reviewed. Substantial dependence on multiple IVDs or other data sources, or by way of example more complex algorithms used for prediction of risk or of resistance or responsiveness to drugs, or bioinformatics pipelines (Section 4.3) involved in assay set-up and analysis may classify as LDTs. The latter are in some countries already certified under ISO 15189 [14]. Inappropriate variant calling and the misinterpretation of the variant effect enriched by the NGS pipelines can dramatically influence the patients’ treatment. For NGS assays working on tumor tissues, clinical cut-offs of acceptability for tumor variant allele frequency (VAF) (%) or HRD scores are not unequivocally defined, impeding to achieve the goal of responding to overall clinical needs [64]. If the intended use of the comprehensive or targeted NGS panels is related to the treatment, bioinformatics pipelines should use appropriate filtering criteria to discriminate

passenger from driver mutations, providing clinically relevant information on the actionability and possible drug treatment of the called-reported variants.

A typical vertical ISO 15189 audit handles this from test request to report, consistent with how the standard and how laboratories treat this as part and parcel of the proper clinical use of the underlying device. Resulting from an overall risk analysis [65], the laboratory has a written policy identifying the need for data integrity, protection against unwanted and malicious loss of data integrity [66], and compliance with the EU General Data Protection Regulation (GDPR) [67], besides regulations on the safe and supervised deployment of big data engines and artificial intelligence [68, 69]. These HI-wide concerns are covered by appropriate service level agreements with the relevant providers. The risk analysis, applying to the complete life-cycle of software [70], summarizes critical changes to the data management infrastructure which need ad-hoc revalidation of the integrity and correct functioning of the system (Table 3).

5 Conclusions and recommendations

5.1 About shared liability, due diligence and intended transparency

As discussed in the introduction, the primary intent of the new legislation is to guarantee safe and clinically effective medical tests on the EU-market. Legal requirements and standards cannot cover in absolute detail the wide range of clinical applications, analytical methods, and HI-specific implementations of care pathways. Absolute legal certainty would reduce flexibility, increase costs and stifle innovation, and thus might be detrimental to the patient.

The new legislation allows for creative interpretations as in many instances it calls for judgements on the appropriateness of implementing clauses. All parties involved have to share responsibility. Parties can demonstrate due diligence by appropriately documenting their decisions. The authors call for the profession to claim its role and take up its responsibility. It also calls for the industry to define and demonstrate the intended use of commercial devices at the fullest, and to give due attention to design and software aspects. While a “restricted intended use” certainly reduces validation costs for the industry, it will shift a self-repeating burden to the individual laboratories and also risks to overload the CAs. The manufacturer’s post market surveillance and clinical follow up is an opportunity to identify shortcomings in the intended purpose of devices, and to update their certificates accordingly. By taking up responsibility, manufacturers have an opportunity to stand out between competitors. Finally, we call for the European and national legislators to ascertain lean implementations reducing administrative burden and timely adjustments as dictated by experiences.

There is little awareness of the IVDR across Europe [11]. The authors call upon the profession to educate the lawmakers on the undesirable side effects of a blind stringent implementation of the IVDR. There is a risk for patient and consumer access to *in vitro* diagnostics (IVDs). Laboratories may become unable to implement all needed LDTs. Also, Europe risks to lose research and development as these activities are likely to move to environments with more lenient regulations.

5.2 ISO 15189 is a sufficient tool for IVDR compliant implementation of LDTs

It is our opinion that the mention of ISO 15189 (IVDR 5 (5) c) elevates it to a harmonized standard. In Table 1, we illustrate the correspondence between elements of the IVDR 5 (5) and clauses in the ISO 15189. In Section 3, we illustrate how standard ISO 15189 conform implementation of LDTs covers these requirements. In Section 4, we illustrate this by way of a selection of special cases. ISO requires concordance with applicable laws. Apparent gaps [17] between IVDR and ISO 15189 can be closed by proper interpretations and corresponding implementation.

Up to now, LDTs were often not presented by the laboratory for incorporation into its ISO 15189 scope, for reasons of absence of standard proficiency testing (PT) schemes and in the case of low volume testing for economic reasons. The ISO 15189 provides for alternatives to PT. With the advent of the IVDR, all LDTs have to conform to the IVDR, and information about such conformity has to be readily available. The laboratory can fulfill this requirement by presenting the LDTs to its AB as a fixed or flexible scope [15]. We favor a flexible scope allowing for generic validation of first-in-class devices. An accompanying technical addendum lists then the LDTs for potential evaluation by the CA.

The CA is competent with respect to the manufacturing process of the devices, the fulfillment of applicable elements of IVDR ANN I, and documentary obligations. Paraphrased, the documentation has to show that a device reliably does what it claims to do. With respect to modifications of existing commercial devices, its competence relates to the argumentation on the need for modifications of the intended use or of the design of the device, the significance of the change and the improved benefit/risk ratio

resulting from the modification. Per May 2028, the laboratories have to demonstrate due diligence with respect to the market exploration for viable commercial alternatives.

5.3 Reduction of administrative burden – use of ISO 15189 accreditation mechanisms

For the implementation of the IVDR, national legislators have to install the CAs mostly by assigning new competences to existing bodies, taking into account their own legislative ecosystem and the organization of the healthcare system. Typically, licensing of HI and laboratories, auditing according to ISO standards, and oversight of pharmaceuticals and medical devices are the competence of different administrations. In some countries ISO 15189 accreditation is a prerequisite for licensing of the laboratory, and in others accreditation is voluntary [14]. In some countries professional organizations are self-regulatory [19], while in others all regulatory initiative comes from relevant authorities. The situation may be further compounded by various degrees of defederalization of the health care system [19], with a corresponding hierarchy of competences, and of primacy of regulatory frameworks. By way of example, in Germany, healthcare is regulated by the "föderierte Länder" and cannot be regulated by national bodies. A quality regime ("RiliBÄk") which essentially mirrors ISO 15189 is mandatory while accreditation to ISO 15189 is voluntary and legally subordinate to RiliBÄk requirements [19]. Obviously, we cannot give a one-size-fits-all advice.

Notwithstanding the above, it is the opinion of the authors that the legislator in interpreting the IVDR has to minimize administrative burdens. Striving for perfection in the legislation might be the enemy of an effective legislation. It is much easier to add elements to a law later, then to scrap superfluous rules. The scope and 2027 end date of IVDR article 111 may come too late to amend unforeseen and unwanted side effects of the regulation. Coordination with other regulations on chemicals and information technology has to be updated in due time.

Under the IVDR (5 (5) g), the national CA can extend its authority to request documentation for non-class D devices. If the national legislator were to make this mandatory, the administrative workload will increase immensely. Also, the CA might be enticed to mimic a NB approach, and ask for notification and approval of planned performance studies prior to their execution. It will add to the administrative burden and delay the putting into use of the LDTs. Also, the CA might ask to report IVDR ANN I compliant safety and performance studies in a pre-determined format. It risks to reduce the validation file to a checklist while not necessarily improving the appropriateness of the validation studies. It is the opinion of the authors that proper risk analysis is a better way to guarantee the appropriateness of the validation files. It requires all parties to share responsibilities (Section 5.1). For the sake of communication with the CA we recommend that the laboratory in its general operating procedures for each element of the validation file refers to the applicable clauses of IVDR ANN I.

Furthermore, and notwithstanding that the CA can at will call for information or do unannounced audits, it would be wise to make maximum use of accreditation programs already in place. The introduction of new regulatory and administrative mechanisms will come with investments of tax payer money. Imposing administrative fees on the HIs corresponds to futile recycling of tax-payer money. The resulting overall opportunity cost for the health care system can be minimized by avoiding duplication of auditing and inspection activities. Solutions will differ by country, as the obligation for medical laboratories to adhere to the ISO 15189 is not universal [14]. In some countries relevant regulatory or oversight authorities are already embedded in AB audits to participate as an observer auditing the applicable specific legal requirements, and/or AB make use of checklists to evaluate specific legally-binding requirements. Embedding the CA into the audit process can be a practical solution. Although laboratories have no choice in it, acceptance of the IVDR will increase when the laboratories can continue to operate in an already existing, familiar and well accepted regulatory space.

5.4 A call for balanced regulation

Calls for additional guidance stem from rightfully perceived incompleteness of the law [71]. Other initiatives are intent on providing generalized approaches to the implementation of the IVDR [16] to avoid every laboratory reinventing the same wheel. As illustrated in Sections 3 and 4, generally applicable guidance will be hard to distill, and the product might draw as much criticism, as the open questions it intends to settle. To be generally applicable MDCG guidance documents should stick to what has to be done, and not to how it has to be done. This also applies to new standards. Thus, these initiatives risk to mostly duplicate existing regulations and guides, without resolving specific issues. Acceptance of additional standards as harmonized standards, may force laboratories to apply for superfluous accreditation. On the other hand, if such initiatives are very specific on the how, then the price we pay for a reduction in

liability is the loss of freedom for reasoned optimized implementations and for innovation.

5.5 Evaluation of equivalence of commercial devices

The evaluation of the presence of an equivalent device on the market (Section 3.1.2, Figure 2) requires a reasoned decision on whether marketed devices meet the appropriate level of performance required in the HI's clinical care pathway (IVDR 5 (5) d). It is the opinion of the authors that this performance criterium should not be restricted to the safety and performance criteria set forth in IVDR ANN I. Non-equivalence refers not only to intended use and predefined performance specifications, but should also be extended to operational, organizational and economic aspects. By way of example of operational considerations, and not limitative, we list here what are also valid elements in the evaluation of public tenders [72]. Implementation of devices according to manufacturer's instructions may not meet turn-around-times requested in the care-programs serviced by the laboratory, or the laboratory does not have access to particular analytical platforms for some tests. Physical footprints and limited financial space can prohibit the implementation of multiple platforms. Manufacturers may not be able to guarantee continuous supply. Not allowing for these valid extended arguments can force the laboratory to reduce their portfolio and will impede optimal patient care. When opting for an LDT, the laboratory shall transparently document its reasoned justification and resort to evaluation and management of the associated risks.

5.6 Evaluation of critical changes to commercial devices

In Figure 2, we introduced the need for a reasoned decision on the criticality of modifications to commercial devices. The MDCG produced a document with guidance on what it considers significant changes in legacy IVD Medical Devices [27]. While this applies to commercial devices and derogations for the transition period between the directive and the regulation, we believe that it can serve as a guideline for the evaluation of the equivalence requirement of the IVDR (IVDR Art 5 (5) d). This double use would ascertain a level playing field for industry and HIs. In table 3, we recapitulate major elements that require a reasoned decision on their criticality, and where appropriate will have to be addressed while validating the LDT for use. It is the opinion of the authors that the profession can take up its responsibility to decide when a modification is minor and the device can be considered to remain a device as intended by the manufacturer, and when a modification will require validation of safety and/or performance characteristics to the extent appropriate for the planned modification, while relying on the manufacturer's validation for other aspects.

5.7 Evaluation of home-made LDTs

Commensurate validation applies to modifications to commercial devices (Section 5.6) and to *de novo* devices developed in the laboratory. The laboratory will resort to its own LDTs mostly, because they fill in niche applications, and there is insufficient interest from suppliers to develop them and to put them into use. By way of an example, we cite here the phenotypic and genotypic identification of long known but rare inherited errors in metabolism. In other cases, niche applications correspond to research interests of the laboratory evolving in innovative translational clinical research. By way of an example, we cite the application of mass spectrometry to the characterization of protein patterns [58]. Obviously, in these examples the original fundamental research will fulfill requirements about scientific validity, and the translational research will document the fitness for clinical use [33]. The validation will have to be supplemented with an analytical validation. A yardstick for the appropriateness of this exercise is whether the documented performance criteria (e. g. traceability and accuracy), will allow future translation to the wider community. Proper peer-review should guarantee this.

The authors believe that the above demonstrates the indispensable role of the medical laboratory professionals in the IVDR roll-out [22]. The IVDR main focus is the manufacturing and putting into use of safe and effective devices, that is prior to the production of individual test results by the laboratory. For the laboratory the manufacture of an LDT device and the laboratory's core business, the use of the device for the production of reliable test results, is one continuous process. The latter is embedded in the clinical function of the laboratory in the hospital or care setting where it engages in consultative services participating in a deliberation dialogue with users about which tests to request, and how to interpret results. Thus, fulfilment of the IVDR requirements comes as a second nature. This is already going on for some decades, gradually being further refined and broadened, guaranteeing fulfillment of all IVDR requirements (among them clinical evidence).

5.8 Putting into use of LDTs

Also, it is the opinion of the authors that the restriction to non-industrial scale of manufacturing of devices, is covered by non-transferal of devices to other HIs (IVDR 5 (5) a). HIs can in-house analyze outsourced samples from other HIs. HIs are allowed to exchange protocols too, which is relevant in case of consortia. A different interpretation would be detrimental to patient care. Indeed, for highly specialized low volume tests reliable analysis and adequate consultative services require minimum critical volumes. Open market principles of the EU also imply that the exchange of services is not hampered by national borders.

5.9 Surveillance plan – maintenance

By means of a surveillance plan, we propose that the ISO 15189 compliant management review provides in a section for the review of changes in conditions surrounding the use of LDTs, in the manufacturing processes and in safety measures, and in performance data and vigilance data (unwanted events and corresponding CAPA). For the sake of inspections by the competent authority it is recommended that this summary is readily available and searchable. Unwanted events have to be traceable to manufacturing and use data [25].

5.10 Off-label and RUO are not part of the IVDR

The use of devices for scientific research or for clinical studies, while not serving a direct diagnostic purpose, are not within the scope of the IVDR.

5.11 Training in regulatory affairs of professionals

The EFLM recognizes a need for dissipation of information on the IVDR, and for specific training on its implementation with respect to LDTs. The EFLM plans to make content available on its e-learning platform.

5.12 Monopolies and patents

New technology almost invariably will be subject to patents, even when they emanate from research partly published in the public domain. Patents create monopolies, and are counter to free-market price setting. The IVDR protects commercial devices against competition from equivalent home-made devices which profit from a relaxed regulatory environment. However, the commission should monitor potential abuse of dominant positions [73].

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