

Opinion Paper

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Implementation of the new EU IVD regulation – urgent initiatives are needed to avert impending crisis

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Abstract: Laboratory medicine in the European Union is at the dawn of a regulatory revolution as it reaches the end of the transition from IVDD 98/79/EC (<https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A31998L0079&qid=1628781352814>) to IVDR 2017/746 <https://eur-lex.europa.eu/eli/reg/2017/746>. Without amendments and contingency plans, implementation of the IVDR in May 2022 will lead the healthcare sector into uncharted waters due to unpreparedness of the EU regulatory infrastructure. Prospective risk analyses were not made by the European Commission, and if nothing happens it can be anticipated that the consequences will impact all stakeholders of the medical test pipeline, may seriously harm patients and may prevent caregivers from making appropriate clinical decisions due to non-availability of medical tests. Finally, it also may discourage

manufacturers and academia from developing specialty tests, thereby hampering innovation in medical diagnostic care. We hereby inform laboratory professionals about the imminent diagnostic collapse using testimonies from representative stakeholders of the diagnostic supply chain and from academia developing innovative in-house tests in domains of unmet clinical needs. Steps taken by the EFLM Task Force on European Regulatory Affairs, under the umbrella of the Biomedical Alliance in Europe, will be highlighted, as well as the search for solutions through dialogue with the European Commission. Although we recognize that the IVDR promotes positive goals such as increased clinical evidence, surveillance, and transparency, we need to ensure that the capabilities of the diagnostic sector are not damaged by infrastructural unpreparedness, while at the same time being forced to submit to a growing bureaucratic and unsupportive structure that will not support its “*droit d’exister*”.

From the EFLM Task Force on European Regulatory Affairs.

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Keywords: CE-IVD tests; competent authorities; EU regulatory system for IVDR implementation; European Commission; expert panel; in-house developed tests; IVDR 2017/746; notified bodies.

Abbreviations: CA, National Competent Authority; CE, Conformité Européenne; CS, Common Specifications; DG SANTE, Directorate-General for Health and Food Safety, European Commission; EC, European Commission; EFLM, European Federation of Laboratory Medicine; EMA, European Medicines Agency; EPSCO, Employment, Social Policy, Health and Consumer Affairs; EU, European Union; EUA, emergency use authorization; EUDAMED, European Databank on Medical Devices central monitored database in which economic operators, medical devices, UDI, Notified Bodies and certificates, vigilance and post-market surveillance, performance studies and market surveillance are included as a mandatory component of the IVDR; EURLs, European Union Reference Laboratories; Expamed, Expert Panel “*In vitro* diagnostic medical devices” for the European Commission; EQA, External Quality Assessment; FDA, Food and Drug Administration; IVDs, *in-vitro* diagnostic tests; IVDD, *in-vitro* diagnostic directive 98/79/EC; IVDR, *in-vitro* diagnostic regulation 2017/746; JRC, Joint Research Centre, the science and knowledge service of the European Commission; LDTs, lab developed tests or in house developed tests; MDCG, Medical Device Coordination Group that advises the EC and is composed of National Competent Authorities and attended by various stakeholders, including Biomed Alliance and EFLM; NGS, next generation sequencing; QMS, quality management system; RUO, research use only; SSP template, Summary of Safety and Performance template; STOA, Panel for the future of Science and Technology of the European Parliament; TGA, Therapeutic Goods Administration, an Australian Government Department of Health.

Introduction

Laboratory testing has an acknowledged widespread role in clinical decision-making, and therefore a direct significance in determining patient management and clinical outcomes. As the famous nephrologist Franz Vollhard said: “*Before therapy, the gods have put diagnosis*”. Consequently, the value of laboratory testing should be considered in the context of its role in setting the course for beneficial actions and patient outcomes. It

is vital that physicians can trust that they are able to choose the best medical test available to help them in their clinical decision-making [1]. An essential precondition is the guaranteed and unrestricted availability of both conventional and innovative medical testing -including companion diagnostics- if “personalized diagnostics” and “precision medicine” are to be promoted.

Laboratory medicine is capable of responding to health care challenges in a timely manner, as can be seen in the current COVID pandemic that has put laboratory medicine and medical testing into the spotlight and amply demonstrated the relevance of medical testing in maintaining public health. Multiple academic laboratories and IVD-manufacturers have invested in the development of different types of COVID tests at short notice to allow market access under the current European IVD Directive 98/79/EC. Unfortunately, as pandemic cases were increasing, the initial focus was mostly on test efficiency rather than test effectiveness as assessment of the latter demands more scrutiny and time [2]. It is important to note that the COVID-19 pandemic has also demonstrated that regulatory systems must be flexible and adaptable, taking into account levels of global risk. Therefore, the FDA in the USA introduced an Emergency Use Authorization (EUA) procedure to speed up the regulatory process as the public health burden caused by COVID-19 required that the regulatory process was “contextualized”.

At the introduction of new tests, medical labs routinely give attention to analytical and clinical performance. There are quasi-standard validation procedures adhered to by national scientific societies, which have proved their value over the years for hundreds of new candidate parameters. Indeed, the field of laboratory medicine is one of the most strictly quality-regulated areas in the whole of medicine, and rightly so, because errors in laboratory diagnostics or assessments can have serious to fatal consequences for patients due to erroneous clinical decision-making that they may initiate. Over the past decades, laboratory medicine has invested enormously in comprehensive quality management systems and diagnostic stewardship in most European countries. As such, the diagnostic sector has regulated itself in a very professional and effective way.

In the past, insufficient testing policies have also revealed tragedies with grave implications for patients leading to e.g. HIV being transmitted to hemophiliacs who routinely injected themselves with concentrate made from large pools of donated plasma, much of which was collected by commercial paid-donor plasmapheresis prior to introduction of routine HIV testing of donor plasma [3].

Transitioning from IVDD to IVDR

To maximize patient safety in the EU the new *In Vitro* Diagnostic Medical Devices Regulation (IVDR 2017/746) for diagnostic tests (known as *in vitro* diagnostic medical devices or IVDs) entered into force on 26 May 2017, with a five-year transition period. The IVDR requires IVD-manufacturers to certify their existing diagnostic tests to comply with the new regulation after the necessary regulatory processes have been installed by the EU Commission and its MDCG. After 26 May 2022, the majority of established commercial CE-marked IVDs can only continue to be marketed if conformity with the IVDR can be declared (for the exception, see “Sell-off Provision” and “Grace Period” below).

As there is no grandfathering for established commercial CE-marked IVDs, routinely used tests all fall under the scope of the IVDR.

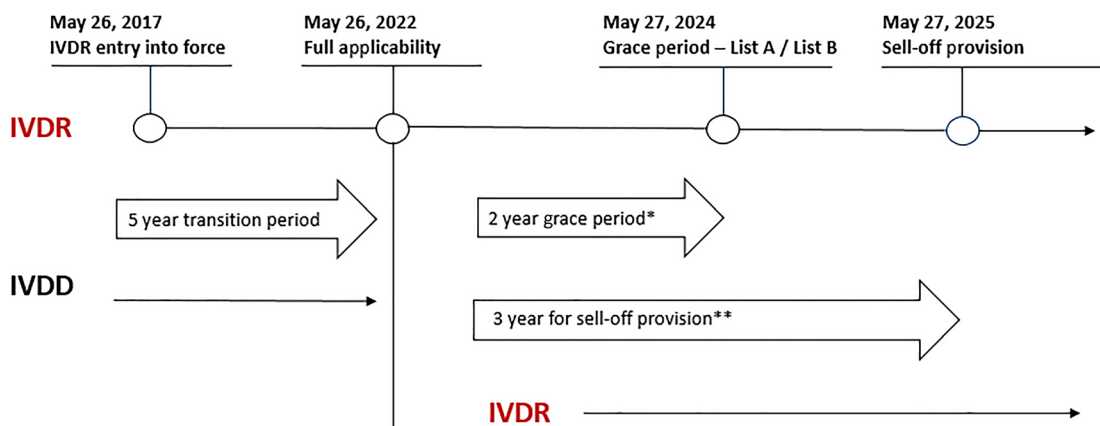
- (1) According to IVDR Article 110 [2] and the so called **“Sell-off Provision”**, CE-marked IVDs that were approved under the IVDD and which have already entered the supply chain before 26 May 2022 may continue to be sold on until they reach the final user (e.g. the clinical laboratory which purchases the IVD) up until 27 May 2025. The usefulness of this provision depends on the shelf-life of the IVDs which are being supplied.
- (2) Only the restricted number of tests included in IVDD Annex II Lists A and B, as well as self-tests with a valid Notified Body Certificate, can take advantage of the **“Grace Period”** (IVDR Article 110 (2) and (3)): these IVDs can continue to be manufactured and placed on the market for a limited period up until 27 May 2024 at the latest. After the Date of Application of the IVDR,

there can be no significant changes in the design and intended purpose of said devices, and they must meet several other requirements of the new Regulation (such as with regards to surveillance, vigilance and registration). After the 26th May 2024, the devices can take advantage of the “Sell-off Provision” if they are already in the supply chain. See Figure 1.

Opportunities

The main aim of the new IVDR is to increase transparency, traceability and effectiveness of testing and to maximize patients’ safety. The IVD Regulation should be considered as a legislative tool for better documentation of the safety and performance of tests in the real world during their entire lifecycle. The key aim is to have a set of rules that are less open to interpretation, and which focus on the entire lifecycle of a medical test rather than up to the point of approval.

May 2022 is imminent and (re)certification under the new IVDR should have been accomplished by now, to make sure that medical tests get their approval according to the IVDR before the end of the transition period. While many of the requirements of the IVDR are the same as under the IVDD [1, 4], a considerable number of new requirements have been added [5]. The IVDR not only governs the medical test and its manufacturer, but also distributors, importers, and authorised representatives (individuals or business entities that act as an authorised point of contact on behalf of an IVD-manufacturer which is based outside of the EU), who all carry legal



* IVDD List A and List B devices with valid IVDD certificates can be further manufactured under specific requirements.

** IVDD devices which have been put in the supplier warehouses before May 26, 2022 and have not reached their final user can be sold until May 27, 2025 latest or until the expiry date is reached.

Figure 1: Transitioning from IVDD to IVDR and consequences for commercial test availability on the EU market.

responsibilities for their activities. The regulation stipulates how manufacturers' quality management systems are to be designed and what they must include for stricter requirements on technical documentation and post-market surveillance – all adding to the emphasis on the test life-cycle. Another change is that all manufacturers, as well as authorised representatives, are required to have a dedicated Person Responsible for Regulatory Compliance with a specified level of relevant training or else work experience corresponding to the training required.

One of the most important changes in the new IVDR is the risk-based test classification system (Figure 2) and the stringent EU Regulatory System (Figure 3). What used to be two limited lists of tests (Annex II, lists A and B) under the

IVDD is now a risk-based classification system where approximately 19,000 medical tests with higher risk require assessment and certification by notified bodies. Medical tests which do not clearly fit into a specific class are automatically classified as class B [5].

Threats

With less than nine months to go before its date of application, medical lab directors seem to be largely uninformed about the availability beyond May 2022 of CE-marked medical tests in their portfolio. Diagnostic providers are seriously concerned about the unreadiness

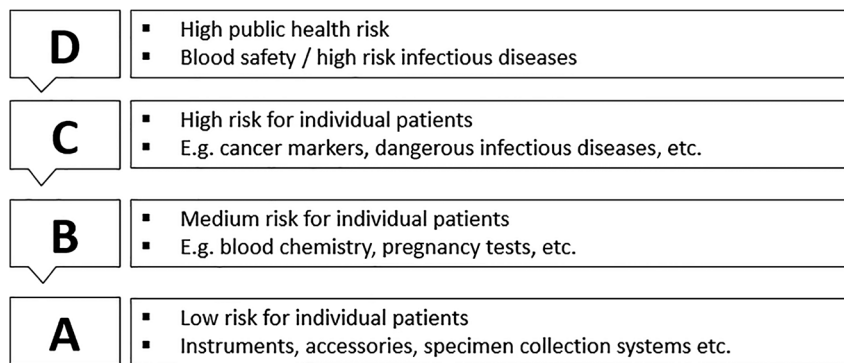


Figure 2: Risk-based classification system for medical tests under the IVDR 2017/746. Medical tests are classified depending on the intended use and the risk that test results bring to patients and/or public health. Non-sterile class A devices are exempted from Notified Body assessment and can be brought on the EU market by self-declaration whereas class A sterile, B, C and D tests all demand Notified Body assessment to check compliance with the IVDR [5].

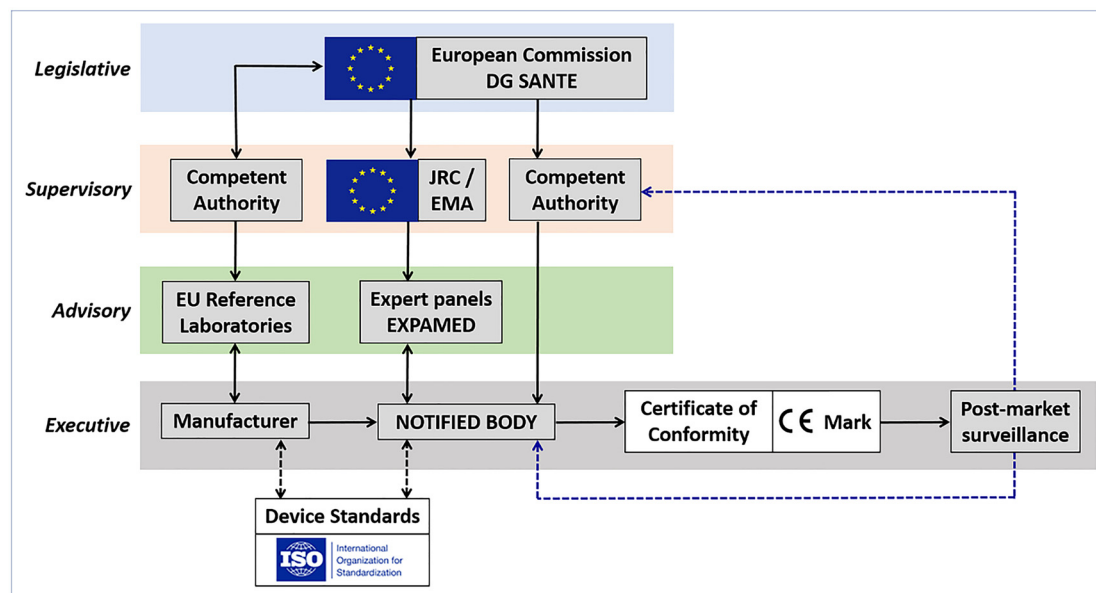


Figure 3: Envisioned conformity assessment process of commercial medical tests by the European Commission.

Manufacturers propose medical test classification based on intended purpose and patient or population risk. For test classes A sterile, B, C, D, the claims are verified by a Notified Body which issues the relevant certificate(s). For class D tests, i.e., the highest risk class, more scrutiny is needed and to that end IVD Expert Panels and European Reference Laboratories additionally are involved during the conformity assessment. For companion diagnostics, additional scrutiny of the suitability of the test by a medicines authority is required (not shown). Note that the functions of the competent authority (which is a single agency in each EU member state, although it appears twice in this Figure) include designation and supervision of both reference laboratories and notified bodies within their country.

of the EU Regulatory System for IVDR implementation and the consequences for timely certification and availability. From May 26th 2022 all medical tests need to comply with the IVDR. This means that the certification pipeline and its infrastructure should have been in full operation by now to allow CE-certification of tests and market access under the IVDR prior to it becoming mandatory.

The impact of the upcoming IVDR requires a transformation of the entire diagnostic sector, including major changes in the conformity assessment process of IVDs. Significantly, the certification process takes 10–13 months on average for most class B and C tests and longer for class D tests (+ approx. three months) and companion diagnostics (+ up to six months). To date, many critical regulatory elements needed to certify IVDs are not in place and important guidance documents are still lacking. This makes it unfeasible for stakeholders to prepare in a timely way for the new regulatory environment and thereby secure continuity of diagnostics beyond May 2022. Should essential commercial tests no longer be available, the affected medical laboratories will have neither the infrastructure nor the material, personnel and financial resources in place to fill in the gaps with in-house developed tests. Particularly, with regard to the financial situation in the health sector in European Countries, it is unlikely that hospital administrations will increase budgets for their laboratories' increased expenditures and effort.

I Facts and figures on IVDR readiness as of May 2021

During the April 2021 workshop on “**The need for better EU Policies for health**” [6], organised by the Panel for the Future of Science and Technology (STOA) of the European Parliament, representatives of the IVD working group of the BioMedical Alliance in Europe, a unique initiative of 36 leading European medical societies which, in combination, include more than 400,000 researchers and health professionals (<https://www.biomedeurop.org/>), stressed that without critical infrastructure, guidance documents and contingency plans, there will be disruption to the availability of essential diagnostic tests, i.e. CE-marked IVDs. To be operational, medical laboratories depend completely on guaranteed diagnostic supply chains that deliver tests in barcoded, tailor-made kits to be run in a fully automated way for a majority of the diagnostic tests provided. The equipment used in core labs often only works with CE-marked tests

on closed instruments, allowing only manufacturer-specific formulations and applications to be run, for liability reasons.

Clear and appropriate guidance is needed for in-house developed tests, also known as laboratory developed tests (LDTs), to help laboratories prepare in time for the new legislation and to support the development of innovative solutions for (niche) emerging applications, rare diseases and rapid responses to health crises. Policymakers should realize that once the guidance is available, enough time is needed to allow laboratories to update their procedures.

The diagnostic sector will be thoroughly transformed by the new regulation. It is up to policy makers and all stakeholders to address the risks that inappropriate implementation of IVDR poses for the entirety of the therapeutic medical sector in Europe. The unreadiness of the EU regulatory infrastructure (insufficient number of active Notified Bodies, unavailability of the EUDAMED database, non-operational expert panels and/or reference labs to evaluate the highest risk tests, lack of contingency plans, delayed guidance documents, poor communication structures to allow for efficient dissemination of strategies) is threatening the EU diagnostic sector and will undoubtedly have serious consequences for patients' lives across Europe in many areas, from emergency medicine to monitoring of therapy.

The main consequences that could be expected are:

- (1) established CE-marked tests face shortages on the European market and/or will disappear with little pre-notification;
- (2) specialty CE-marked tests (for genetics, virology, molecular diagnostics, cancer) will be particularly vulnerable;
- (3) personalised diagnostics and tests for rare diseases will not be developed;
- (4) a polarization towards monopolies in CE-marked tests will reduce diagnostic portfolios and endanger precision medicine and diagnostic innovation;
- (5) the development of new and dynamic solutions for rare diseases and acute health crises such as COVID-19 will be hampered; imagine a 9–12 month certification time lapse during an ensuing pandemic;
- (6) diagnostic laboratories will be unable to re-budget and bear the burden of fulfilling requirements for all their in-house IVD devices/LDTs so may abandon part of their current test portfolio.
- (7) Specialised reference laboratories will be discouraged from using specifically adapted LDTs by the embargo from existing, more generic, CE-marked tests, particularly if the bureaucracy involved in justification of use is prohibitive.

Based on the presentations given during the STOA workshop, the various facets of unreadiness of the EU Regulatory System became crystal clear to the medical experts in the group of attendees (see Table 1). The group rejected the notion that implementation was well on its way. There is serious concern that the European Commission and Medical Devices Coordination Group have not been able to meet their time goals and required legal framework to implement their own regulation.

II Testimonies from key stakeholders (June 2021)

In preparation of this statement and to collect opinions for discussion with EU regulators, we asked laboratory

specialists and manufacturers for their experience of preparing for the IVDR. We reproduce individual anonymized testimonies from selected stakeholders below; these statements confirm the widespread impression that the EU regulatory system is not ready to implement the IVDR.

III Reflections on the looming shortages and/or disappearance of CE-IVDs and in-house tests (status in the second half of 2021)

Less than nine months before the date of application of the IVDR, the above facts and testimonies demonstrate that the

Table 1: Mismatch between EU regulatory provisions and clinical need for IVD medical devices.

Laboratory diagnostic tests essential for clinical practice and care: current status and regulatory provision		Progress towards implementation of the new <i>in vitro</i> diagnostic medical devices regulation (EU) 2017/746 (IVDR)	
CE-marked medical tests			
<ul style="list-style-type: none">– More than 27,000 laboratory diagnostic tests (IVDs) are used in medical practice– Under the EU <i>in vitro</i> diagnostic medical devices directive 98/79/EC (IVDD), less than 10% of laboratory diagnostic tests need to be reviewed by a Notified Body– Eighteen notified bodies are approved to evaluate IVD tests under the IVDD [7]– The process of designating a Notified Body for the EU medical device regulations takes about 700 days– A Notified Body review of an application for a CE-certificate for an IVD test, submitted by a manufacturer, takes an average of 9–12 months for class B and C devices; the process may take 3–6 months longer, up to 12–15 months for class D (without common specifications) and companion diagnostics. Following the review it can take up to a month for the Notified Body to issue the certificate(s).	<ul style="list-style-type: none">–	<ul style="list-style-type: none">– IVDR date of application is 26 May 2022– 90% of IVD tests need conformity assessment by a Notified Body for the first time, under the IVDR. The total is estimated at ~19,000 tests as already ~8,000 tests got lost in transition.– Only six notified bodies are designated so far for the IVDR (situation on 27 August 2021)– Only seven IVD certificates had been issued under the IVDR by end 2020 [8]– Another 249 applications are under review [8]– 78% of IVD manufacturers have reported difficulties getting their IVD tests approved, the main reason given being lack of Notified Body capacity [9]. Other issues were reported such as the pandemic making it difficult to run required performance or usability studies, lack of guidance, NB not accepting applications for class D and companion diagnostics due to lack of infrastructure as well as the risk of prohibitive cost for complying with the IVDR.– CE-marked tests which cannot undergo Notified Body evaluation will no longer be available for patients who need them (with the exception of non-sterile class A devices).	
In-house developed diagnostic tests			
<ul style="list-style-type: none">– In a university hospital survey of laboratories conducting 922 difference laboratory diagnostic tests, 47% were in-house developed laboratory tests; for 72% of these, there was no commercially available alternative [10].	<ul style="list-style-type: none">–	<ul style="list-style-type: none">– Regulatory oversight of laboratory-developed tests has been delegated to EU member states, but guidance has not yet been published– The impact of the IVDR on the availability of laboratory-developed tests needs formal evaluation.– When an alternative test is present, it is generally more laborious and expensive, needing a more robust infrastructure.	

Disclaimer: the content of the Table – initially composed by the BioMed Alliance in Europe for the STOA workshop and partially amended – continuously changes but reflects the situation in the summer of 2021.

A. Testimony of a Clinical Pathologist in a hospital laboratory: “modified CE-IVDs evaluated and documented according to regular ISO-standards should not be considered as LDTs”

“Clinical Chemistry tests make up the vast majority of all laboratory tests. However, nearly all tests are performed on closed systems (such as reagents and instruments supplied by one manufacturer that cannot be exchanged by tests from other manufacturers). With the IVDR, the manufacturer approves a certain test only for selected sample matrices (such as serum or urine). When sample matrices other than the approved ones have to be analyzed, these tests will need a full in-house validation since this test combination will be labelled a LDT. A typical example is amylase testing from body fluids since this test is approved for serum and lithium heparin plasma only, or CRP testing from capillary EDTA-plasma in newborns (which is approved for venous serum and lithium heparin plasma only). Our laboratory performs about 200 different tests in these unusual matrices. Most of these tests are requested rarely but are very critical for these selected patients. Since a full in-house validation will not be feasible for all of these tests, many of these tests would disappear from the test portfolio without substitution. Unlike other rare tests, performing these tests in a reference laboratory will not be possible due to the time lag and/or the instability of the sample for a prolonged transport.

The restriction to certain matrices is a trade-off between demand/revenue and expenses: IVD manufacturers only approve those sample matrices which are used frequently and where the data can be obtained easily. Therefore, the IVDR will be a threat for vulnerable patients such as newborns (due to capillary blood testing) and intensive care patients (due to testing of certain body fluids).

We hope that the IVDR will be postponed and expect that the postponement of LDTs will go in parallel to the CE-marking.”

B. MDCG Working Group OBSERVER testimony: “lack of commercially available alternatives to innovative LDTs”

“Modern medicine is increasingly dependent on sophisticated Medical Laboratory Diagnostics. Increased need for diagnostics is a direct consequence of our improved knowledge about disease processes, increased data procurement and integration, demographic changes and high life expectancies, the increased power of therapeutic interventions and the rapid increase of the number of (candidate) biomarkers capable to provide clinical decision support to the treating physician.

For example, we know approximately 8,000 different rare monogenic disorders that often become apparent early in life or manifest themselves as late-onset diseases. Many patients look back at year-long and painful journeys, until a definite diagnosis is reached for them, particularly for the lower-penetrance diseases or in the context of familial dispositions. Diagnosis depends on specialized expert labs, many of which originated from academic background and scientific interest. These laboratories are scarce, and so is the availability of commercially available tests. To serve patients, specialty labs always have established and validated their own LDT portfolios. As these tests are requested infrequently, and obviously are kept ready until being asked for, there is no market for them, and companies do not develop them as commercial products.

Specifically, without having LDTs for human genetic analysis, well-being is at risk for those carrying a genetic variant or defect, and failure or delay can result in serious and sometimes irreversible damage to their health.

This scenario does not only apply to rare diseases, but is much more common e.g. in modern oncology. In one meeting of BioMed Alliance and EFLM TF-ERA, the representative of a Notified Body was asked about the certification time for an LDT required for common personalized (i.e. directed to tumour-specific mutations and molecular targets) oncological therapy monitoring. In essence, the answer was that “it is a reasonably rapid process requiring just 9 months for certification”. It is difficult to envisage how to communicate this waiting time to a cancer patient who suffers from systemic cancer and receives extremely expensive biological therapy requiring monitoring of therapy failure and tumour relapse.

Having LDTs provided by skilled (and usually accredited) labs does not sacrifice the quality of testing. Indeed, in all EU countries, rigorous internal quality controls and external quality assessments (EQA) and Quality Rounds are available and are even mandatory in most countries. Participation in regular EQA is monitored by notified bodies, national Medical Councils and/or EQA organisations that are themselves accredited. In many countries, specialty diagnostics require the status of a lab accreditation. Quality certificates for correct analyses are issued to laboratories on the criteria of analytical validity, precision, and also in technical or medical interpretation. Quality certificates are issued electronically and can be traced. Failure to pass EQA rounds is sanctioned by revoking certification to offer the test for patient care, thus allowing to easily put in place a comprehensive quality structure for the benefit of patient safety without sacrificing LDTs.”

C. EFLM Task Force European Regulatory Affairs member testimony: “lack of sufficient professional awareness and/or involvement across EU-member states”

“The awareness of the challenges to be faced by the routine diagnostic laboratories not so far in the distant future is bipolar. There is a huge communication and awareness gap regarding the IVDR. This is true for various member countries of the EU regardless of the fact that it shall be universally applicable to the activities of all. This is best illustrated by the lack of input from various EU Laboratory National Societies to the activities of the EFLM TF ERA. The EFLM TF ERA commenced its activities in November 2020 after some preparation period. It has an online platform dedicated to improving visibility of its activities with strong encouragement for input from various National Societies. There is a general notion that compliance with the IVDR achieved by a particular manufacturer in a particular EU country would be readily applicable to all. Whether this is to be the case is to be witnessed in the future, but the general apathy towards the IVDR presently may have far reaching consequence for laboratory diagnostics in all EU member states. Much of the indifference can be traced to communication issues on various levels.”

D. EXPERT PANEL MEMBER testimony: “delays in setting up operational expert panels”

“On 10 September 2019, the COMMISSION IMPLEMENTING DECISION (EU) 2019/1,396 of 10 September 2019 laying down the rules for the application of Regulation (EU) 2017/745 of the European Parliament and of the Council as regards the designation of expert panels in the field of medical devices stated that the “Expert panels were to be designated in order to provide scientific, technical and clinical assistance to the Commission, the Medical Device Coordination Group (MDCG), Member States, notified bodies and manufacturers in relation to the

(continued)

implementation of Regulation (EU) 2017/745 and in order to provide views in accordance with Article 48(6) of Regulation (EU) 2017/746 of the European Parliament and of the Council”.

In this regard, some groups of experts were identified and after some meetings held both in Brussels/Belgium and in Ispra/Italy, the definitive list of groups was designated in specific areas including *In-vitro diagnostic medical devices (IVDs)* to fulfil the tasks set out in paragraphs 9 and 10 of Article 106 of Regulation (EU) 2017/745 and in paragraph 6 of Article 48 of Regulation (EU) 2017/746.

After this step, we held at least three training courses, each requiring two full days in Ispra for the training on the MDGC-IVDR group, to exchange opinions, competences and to harmonize the metrics of our future job as future candidate members of these nascent expert working groups. On January 29th, 2021, all members of the IVDR expert panel received a letter from the secretariat stating the IVD panel had not yet been constituted.

Only in May 2021 the SANTE-Expanded Secretariat started the procedure for electing a chair and vice-chair of the IVDR panel.

I realized in that precise moment as, also due to the COVID pandemic, nothing was working in favour of the IVDR expert panel: while the rules were becoming effective, no activities were spent in support of the revision of IVD products, particularly class D, although many products for COVID diagnostics were launched in the market as CE-IVD under EU setting. Nonetheless, also for genomic products there are many concerns because they have been considered as a topic to cover in the next years, after the new IVDR will enter into force. The market of genomic testing is dramatically growing particularly after the implementation of next generation sequencing technologies (NGS) in clinical routine diagnostics. As an academic molecular geneticist, I am really worried due to the following reasons: a) the market of genomics and molecular biology is mainly based on the use of RUO chemicals and kits; b) NGS pipelines are generally RUO and, only in a few cases, coupled with the use of CE-IVD bioinformatics pipelines; c) when the reagents are CE-IVD marked, the instruments on which they are run are not CE-marked; d) 95% of the instruments for pipetting, handling, extraction are not set up according to IVD certification rules. The real risk is having to work in a spurious system in which either only the analyser, or the software or some reagents will be in compliance with the new IVDR. Therefore, I am wondering whether beyond May 2022, I should stop providing molecular testing for: a) cancer patients needing targeted treatments administered after the molecular profiling of their tumour or germline DNA; b) patients with severe metabolic conditions, needing the molecular diagnosis of their defect; c) in the case of SARS-CoV-2, could we continue to perform either real-time PCR-based screenings or sequencing for the tracing? If the IVD companies need to re-register their entire IVD portfolio under the new regulation, and it is really difficult considering that only seven IVD certificates have been approved under the IVDR so far, think about how destructive the effect could be if all this has repercussions on the market of RUO reagents and instrumentation in the vast field of genomic diagnostics (both human and microorganisms). While the European Commission (EC) is taking all the time to organize the expert groups, the NBs continue to be so few and the delays in submitting assessments and performing auditing by the expert panel will have dramatic effects on the future workload of the experts. This is even more so because the guidance document for sustainable EU-wide regulation for home made and academic tests is not yet available, considering that for 72% of about 50% of molecular tests there is no commercially available alternative. Therefore, the local institutions and ministries of health of each country should urgently take a common position in order to guarantee continuity of patient diagnostics and care, as well as patient safety, and should ask the EC for solutions.”

E. IVD-INDUSTRY testimonies: “lack of an operational EU regulatory infrastructure with sufficient notified bodies and other key elements needed for safe IVDR implementation” IVD manufacturers have expressed concerns regarding the readiness of the regulatory infrastructure. The main challenges are the availability and capacity of Notified Bodies, the non-operational Class D infrastructure, the negative impact of the pandemic, and a general absence of EU-level guidance on how to comply with the IVDR. Below are statements that several manufacturers made in response to the survey question: “Are there any issues that prevent you from starting or completing certification under the IVD Regulation?”

IVD Manufacturer (A): “Our current Notified Body has applied a long time ago, but is still not designated under the IVDR and there is significant uncertainty when this will happen. Having to change the Notified Body on short notice would be another even more significant obstacle. To receive approval prior May 26th, 2022, we expect that we need to submit our technical documentation to a designated Notified Body ~9 months ahead of time, meaning by end of August 2021. Looking at the time course for designation of the only four designated Notified Bodies, we see a high risk that our Notified Body will not be designated in time.

Many guidance documents are still missing (most important for us: Performance evaluation, SSP template and guidance, Post-Market Surveillance requirements) which results in uncertainty in interpretation of the regulation. COVID-19 and its effect on our business and operation still is a major general obstacle for preparation for IVDR.”

IVD Manufacturer (B): “It is currently impossible to achieve IVDR compliance for Class D products as there are no EURLs, CS or Expert panels. Beyond that, the time involved in the Notified Body Technical documentation review and QMS audit is roughly one year. The delays in publishing guidance documents for key areas of the regulation meant delays and rework for our remediation teams. Thus, the timeline is extremely tight to complete the Notified Body review, and then to try to implement the changes on a worldwide scale without interrupting the flow of product to market.

In addition, inconsistent interpretation of the IVDR from one Notified Body to the next has required major strategy shifts that have far-reaching consequences and rework of already remediated files.”

IVD Manufacturer (C): “The previous ISO 13485 certification body didn’t apply for the IVDR or didn’t get accredited yet. This implied a one year process to identify the new Notified Body and to transfer ISO 13485 and IVDR QMS certification. The finalization and signature of the contract with the new Notified Body required 4–6 months from the manufacturer’s application.

Reaching agreement on the classification of some devices took multiple rounds of communication with the Notified Body. The publication of the “MDCG 2020-16 Guidance on Classification Rules for *in vitro* Diagnostic Medical Devices under Regulation (EU) 2017/746” in November 2020 was helpful to reach a final agreement.

(continued)

The complexity of the new conformity assessment is requiring more time and resources than initially planned. The lack of guidance documents and experience of both the manufacturers and the notified bodies in the conformity assessment of “devices other than those covered by Annex II” under the IVD Directive, is resulting in a longer learning curve and is requiring multiple revisions of technical files.”

IVD Manufacturer (D): “Of all our IVDD products (small manufacturer) 87% will be discontinued for the EU. Many of these had low sales volumes, but the cost of NB fees has been a significant factor, as is the human resources to complete the documentation.”

IVD Manufacturer (E): “There is a very short period for transition due to the following facts that are complicating all situations:

- problem of availability of implementation acts
- limited number of Notified Bodies certified according to IVDR (therefore NBs will be overloaded and assessment period for technical files assessment that NBs can declare is still prolonging)
- problem of COVID situation – this is also the core fact complicating and delaying preparations (number of employees ill, or in quarantine, or needing to stay at home with children because of closed schools) – even if our company hired further resources and makes maximum to be prepared in time, the transition period is still too short, depending also on the capacity of our Notified Body. We can only hope that we will manage to comply for all the products in time so that our sales are not threatened much.”

EC and MDCG have not succeeded in putting in place the EU regulatory system in time to safely implement the IVDR (Table 1) [7–10]. We consider the current state flawed in such a way that we recommend postponement as the only logical consequence. What is the alternative? No regulatory approval for thousands of tests without which health care would not function in a pandemic situation. No EU politician or administrator will dare to take the responsibility of dismantling a working health care system. It is in the interest of the EU to maintain its healthcare industry and IVD-companies and their market. It is inconceivable that tests will not be allowed in the EU and that countries around the globe which trust in the CE-marking would also suffer since they rely on EU-sourced medical tests. Indeed, the IVD sector is one of the only European manufacturing sectors left with a positive trade relationship with China. If there is a shortage of EU IVDs then this would definitely impact many other countries around the globe. Dismantling will have consequences for customers in addition to the effects it has on patients.

Today, the infrastructure for the very high-risk tests (“class D”) is almost entirely missing. These include tests which are of critical importance to healthcare systems because they are needed to screen the European blood supply, check cells and organs for transplantation or manage outbreaks of infectious disease, such as the COVID-19 pandemic. Aside from the six notified bodies designated so far, common specifications, the IVD expert panel and appropriate EU Reference Laboratories are lacking. Because of this, the EC allows NBs to evaluate class D tests without the guidance of the IVD expert panel/EURLs. Yet, NBs are hesitant about this situation and refused so far to evaluate class D tests without being backed up by the expert panel/EURLs (Figure 3). This is understandable, as NBs are risk averse and do not like to give non-binding guidance on medical tests for the obvious reason of liability. Therefore, if nothing happens, the IVDR

may be in place only for the lowest risk devices (e.g., instrumentation, general culture media, etc.) with an uneven, incomplete spread of reagent kits in other classes.

At a meeting of the European Council (of health ministers, EPSCO) on June 15th 2021, 15 ministers of health brought the critical IVD-situation to the attention of the EC and the MDCG. This provides the EC with a formal mandate to find solutions and/or make contingency plans. Due to this intervention, transition measures will be taken to ensure the continuity of commercial tests, however it is not guaranteed that the same prolongation will be given for in-house developed tests. There is a risk that laboratories might still have to be compliant per May 2022 for in-house developed tests. A grace period and/or postponement for in-house developed tests is as crucial as for CE-IVDs, particularly if there is no EUDAMED database and if there is an impact on availability of CE-IVD kits. The time gained should be used in a sensible manner. Specifically and from our perspective appropriate diagnostic experts should be prominently involved and their views given priority, even when they take positions straying from the fixed process governed by non-experts, as we have witnessed up to now. The EU regulatory infrastructure should first be made operational, since implementing the IVDR while the regulatory infrastructure is still being built is disruptive for the diagnostic community and for individual patient management.

Laboratory professionals need to bring in sound arguments and draw attention to the issues around in-house tests, in order to create a similar ground for sustainable solutions as for the CE-IVDs manufactured by the IVD-industry. Possibilities for in-house testing should be protected during transition of the CE-marked sector, both as a safety net and to avoid additional gaps in the diagnostic portfolio. Recognition of diagnostic reference laboratory expertise should also be integrated, in order to avoid monopolies in rare disease and personalised diagnostics which may stifle further improvement.

The preparedness of the medical laboratories in the EU is currently surveyed by BioMed Alliance and EFLM as the awareness regarding the impact of the IVDR for both CE-IVDs and LDTs apparently differs among EU member states. The survey data are not yet available. In other parts of the world such as Australia, the Australian regulatory authority TGA has done nothing to increase regulation of IVD tests. While in-house IVDs are catalogued, they do not have enough expert resources to evaluate them, not even through the accreditation system. As the infrastructure and resources needed to meet the motivation of global regulatory directives are simply not established, and the COVID pandemic is still a priority, it will take many more years to prepare the EU regulatory system for the IVDR.

Laboratory medicine is one of the most strictly quality-regulated areas in all of medicine, enabling *state-of-the-art* clinical decisions based on objective, reproducible, safe, and effective lab test results. From EQA report sheets, every lab can see how its own performance is in comparison to other (anonymized) participants with respect to all benchmarked EQA parameters within a given EQA scheme. Therefore, besides their value for transparent quality reporting, EQA programs also can be seen as efficient regulators of the market, because test methods that are inferior and at the origin of repeated EQA failures, are easily identified amongst the plethora of methods available for a given biomarker. As passing EQA rounds is mandatory for the right to practise, quality will rule and the lack of it will lead to inferior tests being identified and retracted from the market. There is certainly leverage in using this quality instrument to warrant patient safety in diagnostics.

It is generally recognized that about 70% of clinical decisions made by caregivers in peripheral and academic hospitals are based on diagnostic test results. Therefore, the supportive tools -i.e., medical tests, including CE-IVDs and in-house developed tests- are crucial and should remain unabatedly available and accessible on the European market in their current formulations till the new EU regulatory system is in place and adequate implementation of the IVDR is feasible.

IV In search of solutions for the medical laboratory sector

After the June EPSCO meeting, where ministers of health expressed their concerns regarding the issues around IVDR implementation, the EU Council Conclusions on Access to medicines and medical devices for a Stronger and Resilient

EU became publicly available (<https://data.consilium.europa.eu/doc/document/ST-9750-2021-INIT/en/pdf>).

The EC now needs to reflect on the next steps to take. Guidance from and dialogue with lab professionals is needed to find solutions on how to preserve and support diagnostic laboratory medicine and the test supply chains for creating actionable test results in patients across healthcare systems. Essential starting points for proper IVDR implementation are (a) having in place a minimum acceptable regulatory infrastructure; (b) encompassing all IVDs which need a NB certificate; and (c) ensuring that all IVDs can be certified and transition in a timely way which ensures that full test menus remain available to diagnostic laboratory medicine.

Which scenarios might be considered by the EC for **commercial CE-IVDs** after the successful awareness campaign in the June EU council meeting? Firstly, there is the one-year postponement precedent from the MDR 2017/745 although one year postponement is nowhere near sufficient for the complex IVDR. Ideally, the test (re)certification process should start after the complete infrastructure is in place, so a longer postponement with undefined date of application is needed. Alternatively, one could consider extending the grace period for all IVDs that need to undergo NB assessment. At least three to four years expansion should be the aim to avoid bottlenecks such as the end of the MDR grace period in May 2024 and because class D tests and companion diagnostics need 16–18 months to be certified. As MDR got an extended grace period, why not give the very impactful and new IVDR a later expansion date? The drawback of extending the grace period is that the grace period option freezes innovation and medical test improvement. Freezing of test improvements must be avoided by an opening clause to allow further development of established tests to achieve the best possible performance. Finally, a mixture of the above scenarios, i.e., postponement with an expanded grace period, is also a possibility, as long as the timelines are similar and parallel for CE-IVDs and LDTs.

Alternatively, the EC could produce and legally implement a Common Specification for certain IVDs (in analogy to similar procedures for the MDR), for example stating that meeting certain EQA-standards would be sufficient. That would make a long NB review and expert panel review unnecessary if there is a published EU Common Specification, and the medical test meets all of its requirements.

Professional societies and lab specialists should map the preparedness of medical laboratories and the issues that they encounter in relation to the implementation of the IVDR per May 2022 for **in-house developed tests**, according to

the requirements of Art 5.5. in the IVDR [5, 11, 12]. To that end, the BioMedical Alliance in Europe conducted a survey in summer 2021 with a representative sample of medical labs serving different diagnostic disciplines. The outputs of the survey should help to provide insight into the current degree of preparedness and the issues that medical laboratories encounter. Secondly, the survey results will help to establish solid arguments for postponement and/or other solutions to safeguard the continuation of in-house developed tests. Moreover, it is anticipated that the outputs are likely to reveal the parallel need for preparation of the EU regulatory infrastructure ahead of the implementation of Art 5.5 for in-house developed tests. The EU should take advantage of the excellent professional infrastructure and concepts available within the BioMedical Alliance in Europe, which represents a broad spectrum of today's medical societies. Speaking for laboratory medicine, TF-ERA is the operational arm of EFLM within the BioMedical Alliance in Europe and has developed strategies to support improving the steps to be taken for the IVDR implementation.

In conclusion, we value the efforts of the EU Commission to further increase patient safety and clinical effectiveness of diagnostic services but the goal will not be met by imposing blanket regulatory requirements which mean potential disruption of all medical tests indiscriminately. Until now, the process has not involved enough professional laboratory expertise to ensure success and the EC does not appear to be aware of the long-lasting high degree of safety, effectiveness and quality assurance in the diagnostic sector. A failed start and baseless bureaucratic burden will not only harm patients, hurt medical laboratories, but also impede laboratory medicine development for years to come, increase diagnostic costs, and erode diagnostic innovation in Europe. Until the EU Regulatory System is comprehensively reworked and operational, patient safety must be considered to be in danger far beyond the transition time. Sustainable accommodations must be made to the IVDR to prevent collapse of a well-functioning diagnostic sector. Also, the IVDR should be interpreted against the background of already guaranteed quality of diagnostic services in ISO-accredited labs (often ISO 15189:2012) by EC4 registered laboratory specialists, with active participation and guidance of professional societies, who are fully aware of the interest in optimising the whole diagnostic chain.

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