The *In Vitro* Diagnostic Regulation in Europe: Implications for Precision Medicine and Pharmaceutical Development

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Abstract

An estimated 70% of clinical decisions are based on the results of *in vitro* diagnostic (IVD) tests. IVD devices such as companion diagnostics (CDx) are essential in precision medicine to improve patient outcomes by identifying patients who are most or least likely to benefit from a corresponding medicinal product. In Europe, these tests will be regulated under the new in vitro diagnostic regulation (IVDR) which comes into full effect in May 2022. The Regulation introduces significantly higher regulatory requirements for CDx and in-house biomarker tests, often currently used for patient selection decision making, than the current IVD Directive. IVDR planning has been challenging while the European Commission has dealt with major complex hurdles including the COVID-19 pandemic, Brexit and the EU Medical Device Regulation (MDR), leading to delays in its implementation. While the intent of the IVDR is to improve quality and safety of IVDs and increase transparency and traceability of devices, the lack of readiness of the new regulatory framework may severely restrict the availability of CDx devices and in-house tests after May 2022. Case studies show that reduced biomarker test availability will limit access for thousands of patients to the innovative precision medicines that they need. This article describes the various challenges of IVDR implementation for CDx devices and in-house tests and the likely impact that this will have on patients across the European Union and briefly discusses what actions should be taken into consideration as stakeholders prepare their current portfolio of CDx products and plan studies, approvals and launch of future targeted therapies.

Introduction

An estimated 70% of clinical decisions are based on the results of *in vitro* diagnostic (IVD) tests.[1] IVD devices such as companion diagnostics (CDx) are essential in precision medicine to improve patient outcomes by identifying patients most (or least) likely to benefit from a corresponding medicinal product. In fact, CDx assays have revolutionized the field of personalized medicine where the success of most targeted oncology therapies relies on an accurate and reliable predictive biomarker to ensure their safe and effective use in the right patient population.[2,3,4] In the past 20 years there has been a steady increase in the number of CDx devices developed and approved for use with a targeted medicine. Data available from the US Food and Drug Administration (FDA) show that 44 CDx assays were approved by the end of 2020.[5] The increase in CDx approvals mirrors the surge in targeted oncology therapies, and these numbers will continue to increase with advances in new and innovative medicines in other therapeutic areas as our understanding of the molecular mechanism increases to grow.

The European Commission has also committed to prioritizing cancer prevention, treatment, and care. The recently published Europe's Beating Cancer Plan put forward a new EU-supported Cancer Screening Scheme to help Member States ensure that 90% of the EU population who qualify for breast, cervical and colorectal cancer screenings are offered screening by 2025.[6] While the FDA has a clear path for the co-development and approval of a biomarker test with a corresponding therapeutic, regulatory agencies in Europe have currently not defined a similar path, resulting in a lack of clarity for CDx-specific performance expectations for critical aspects of device performance (e.g., clinical evidence). Moreover, the current EU regulatory processes for devices and drugs do not align to enable concurrent approval of the diagnostic and the medicine, resulting in a potential gap before the CDx could become available to patients.

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'**Companion diagnostic**' means a device which is essential for the safe and effective use of a corresponding medicinal product to:

(a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or

(b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product

Figure 1: IVDR Definition of Companion Diagnostic

The regulatory framework for CDx in Europe is being introduced in the new *In Vitro* Diagnostic Regulation (IVDR, legislated on 26th May 2017[7], applies fully on 26th May 2022) replacing the existing IVD Directive (98/79/EC; IVDD).[8] For the first time, CDx devices are defined and regulated by designated notified bodies with clear requirements on vital aspects of device performance and oversight to ensure that the quality, safety, and performance of these devices is appropriate for their intended purpose. Unlike the IVDD, IVDR regulates in-house tests offered by Single Healthcare Institutions (SHIs – e.g., organizations such as hospitals, clinics, and laboratories). As much testing for precision medicine is currently conducted using tests performed at SHIs, the implementation of the IVDR may have a profound impact on the ability to generate results for critical treatment decisions.[9] This article highlights the challenges and implications of IVDR for CDx devices and in-house tests in precision medicine that would now take into consideration diverse stakeholders – device manufacturers, health institutions and the pharmaceutical industry – suggesting a path forward to prepare for the new Regulation.

In-vitro diagnostic regulation – key changes and their implication for precision medicine

The new regulatory framework introduces key changes for IVDs in Europe[10], including a rule-based (re-)classification system where most devices will now require conformity assessment by a designated notified body (**Table 1**). Importantly, the Regulation provides a definition for CDx devices (**Figure 1**) and places them as Class C, the second highest risk category. CDx devices will need to meet more stringent requirements on clinical evidence and post-market surveillance. CDx devices will also have a new conformity assessment pathway that includes a consultation process between the notified body and the medicine regulatory authority or EMA. This step provides a critical link between the assessment of the CDx and the assessment of the corresponding medicinal product. In addition, the Regulation will have a major impact on laboratory developed tests (LDTs), also known as in-house tests, which are out of scope of the IVDD but will need to meet the general safety and performance requirements laid out in Annex I of the IVDR.[11]

Table 1: Classification categories for IVDs under IVDR

Category	Class D	Class C	Class B	Class A
Risk Description	High public health risk, high personal risk	High personal risk, moderate to low public health risk	Moderate to low personal risk, low public health risk	Low personal risk, low public health risk
Device Examples	• HIV 1/2 • Hepatitis C virus • Hepatitis B virus • Blood grouping ABO, Rhesus (including RHW1), Kell, Kidd and Duffy systems	• Rubella • Neonatal screening for metabolic disorders • Blood gas analyzers • Companion diagnostics • Genetic tests • Cancer markers • Self-tests	• Thyroid function • Infertility assays • Clinical chemistry • Self-test devices that are not Class C (pregnancy, fertility, cholesterol and urine tests for glucose, erythrocytes, leucocytes and bacteria	• Accessories • Wash buffers • Specimen receptacles • Instruments • Culture media

Challenges and Impact of IVDR

CDx devices – diagnostics for medicinal product treatment decision making

Despite a five-year transition period to prepare for IVDR, planning has taken a backseat with limited resources available, thus leading to delays in implementation while the European Commission has dealt with major complex hurdles (including the coronavirus pandemic, Brexit, and the EU Medical Device Regulation (MDR). The IVDR is far more comprehensive than the IVDD in its requirements (**Figure 2**) to improve quality and safety of IVDs and increase transparency and traceability of devices; as a consequence, the transition so far has been challenging. Under the IVDD, only ~15% of devices required certification by a notified body, the remaining 85% of devices are self-certified to conform to the essential requirements by device manufacturers.[12]

"Critically for CDx devices, the conformity assessment procedure, including a process for interaction between the notified body and the medicines authority and the requirements of the sponsor is yet to be established."

Overhaul of device classification under IVDR will result in the up regulation of many IVD types, including CDx tests. Consequently an estimated 80-90% of IVDs will require assessment and (re) certification by an IVDR-designated notified body by the date of application to remain on market or in service within the EU.[12,13] With the date of application fast approaching, the healthcare industry and key stakeholders have raised serious concerns that the regulatory infrastructure is not yet ready. At the time of writing: only five of the 22 IVDD notified bodies are designated for IVDR conformity assessments;[14] expert panels and approved reference laboratories required for high class device assessments are lacking; implementation of the EUDAMED database is delayed; and many essential guidance documents for interpretation and implementation of the requirements are pending.

Critically for CDx devices, the conformity assessment procedure, including a process for interaction between the notified body and the medicines authority and the requirements of the sponsor is yet to be established. Guidance on key topics such as the continued use of biomarker assays in ongoing clinical trials of a therapeutic product(s), and processes for seeking scientific advice regarding the diagnostic in a therapeutic clinical study and accelerated approval are still not published.[15]

During the transition interim, device manufacturers have continued to plan for IVDR re-certifications as best they can. Despite these planning and execution efforts, reliable reports indicate that notified bodies are so overwhelmed with the volume of IVD applications that they are rejecting new applications. For example, in the case of COVID-19 diagnostics, some notified bodies are not accepting applications due to capacity limitations.[16]

Data from MedTech Europe (personal communication) indicate that conformity assessment

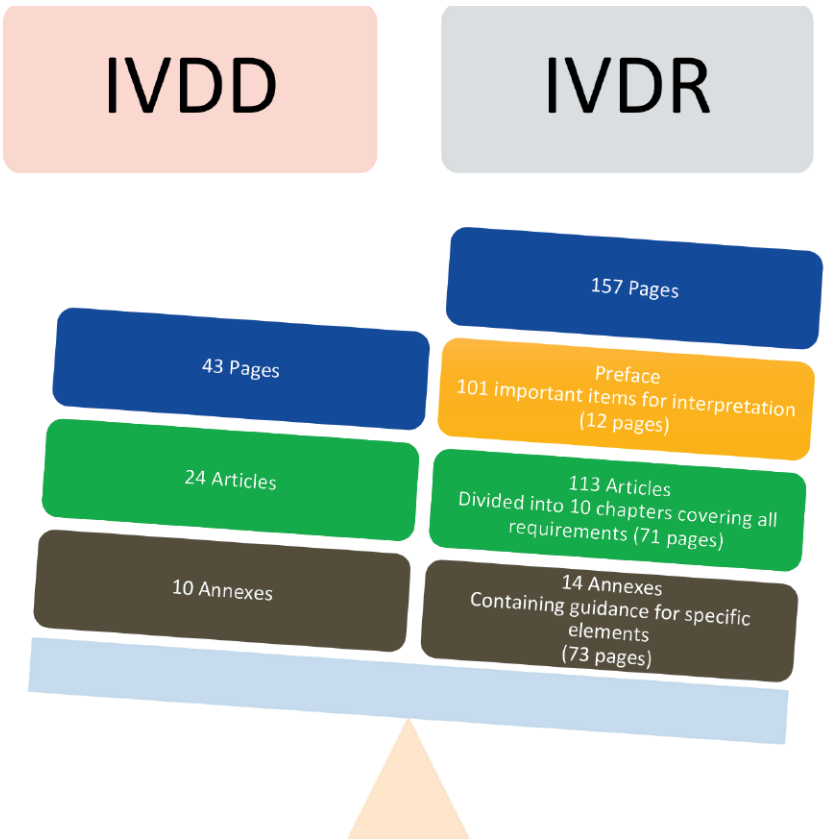

Figure 2: IVDD versus IVDR – IVDR is more comprehensive than IVDD

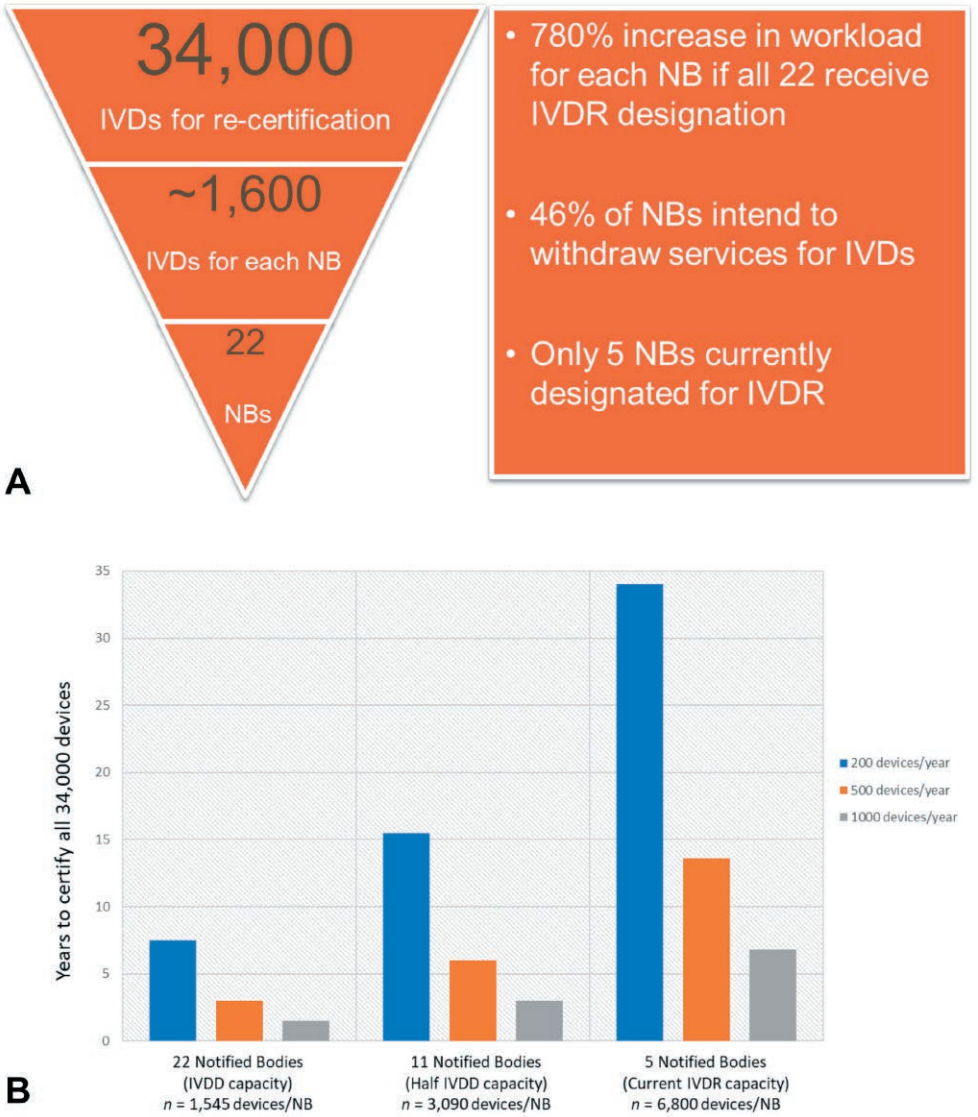

Figure 3: (A) Numbers of designated notified bodies and their potential capacity, and (B) projected time required for IVD re-certifications

Table 2: Shows provides the detailed requirements for the health institution exemption for in-house devices under Article 5 paragraph 5 of the IVDR

The health institute justifies in its documentation that the target patients group's specific needs cannot be met, or cannot be met at the appropriate level of performance by an equivalent IVD available on the market (including CE marked commercially available IVDs);
The IVD is not transferred to another legal entity;
The manufacture and use of the IVD occurs under appropriate quality management systems;
The laboratory of the health institute is compliant with ISO 15189 or where applicable national provisions, including any national provisions regarding accreditation;
The health institute provides information upon request on the use of such IVDs, to its national competent authority, which shall include a justification of their manufacturing, modification and use;
The health institute draws up a declaration (publicly available) some of this information on their IVD; including name and address of the health institution, details of the IVDs and a declaration that the IVD meets the relevant General Safety and Performance Requirements;
The health institute ensure that all the necessary technical documentation for the IVD is in place;
The health institute reviews the performance of the IVD and takes any necessary corrective actions.

of Class B/C devices is currently taking 9-12 months and could take up to 18 months (or longer) for CDx devices. CDx manufacturers are now facing the stark reality that their devices will not be re-certified by the date of application. Considering that 34,000 of the 40,000 existing IVDs will require re-certification by a notified body,[15] MedTech Europe speculated that if all 22 IVDD notified bodies applied for IVDR status, each "would on average need to assess at least 1,600 IVDs", equating to an increase of 780% in NB workload[17], suggesting that notified bodies have a 'normal' capacity to certify ~205 devices/year at maximum. However, almost half of surveyed notified bodies indicated that they will not pursue IVDR designation.[17] To understand the impact of these challenges on IVDR device certifications (**Figure 3A**), we modelled the workload and capacity available for notified bodies to estimate the potential time needed to re-certify all IVDs on the European market.

As shown in **Figure 3B** in a scenario with 11 designated notified bodies, each with capacity to assess ~200 devices per year, the industry may require over 15 years to re-certify all existing IVDs. If we assume that only half or a quarter of IVD technical files will be sampled for notified body review, then this timeframe could be cut to 7.5 and 3.75 years, respectively.

Consequently, the lack of readiness of the new regulatory framework and limitations in notified body capacity and resource may severely restrict the availability of IVDs and more importantly CDx devices and in-house tests for patient selection after May 2022.

We conducted a further modelling exercise to understand how reduced CDx availability due to notified body capacity limitations and other missing elements in the regulatory infrastructure translates to patient impact in the EU. Our analysis, illustrated in **Figures 4 and 5** and explained below, considers the impact of reduced biomarker testing in oncology patients requiring personalized medicine if the current IVDR date of application goes ahead as planned. Referring to Global Cancer statistics, informed by the International Agency for Research on Cancer and Project GENIE[18], we considered estimates for the number of patients diagnosed in 2020 and estimated for 2025 for our modelling. Based on these figures, 320,839 (2020) or 340,386 (2025) accounting respectively for 7.3% of new cancer patients would be eligible for an approved precision medicine (PMRx).[19] Even if we were to conservatively estimate that CDx testing is impacted for only 10% of these patients this would predict that over 32,000 approved PMRx patients would be denied access to their potential precision therapy based on 2020 figures, rising to over 34,000 based on estimates for 2025

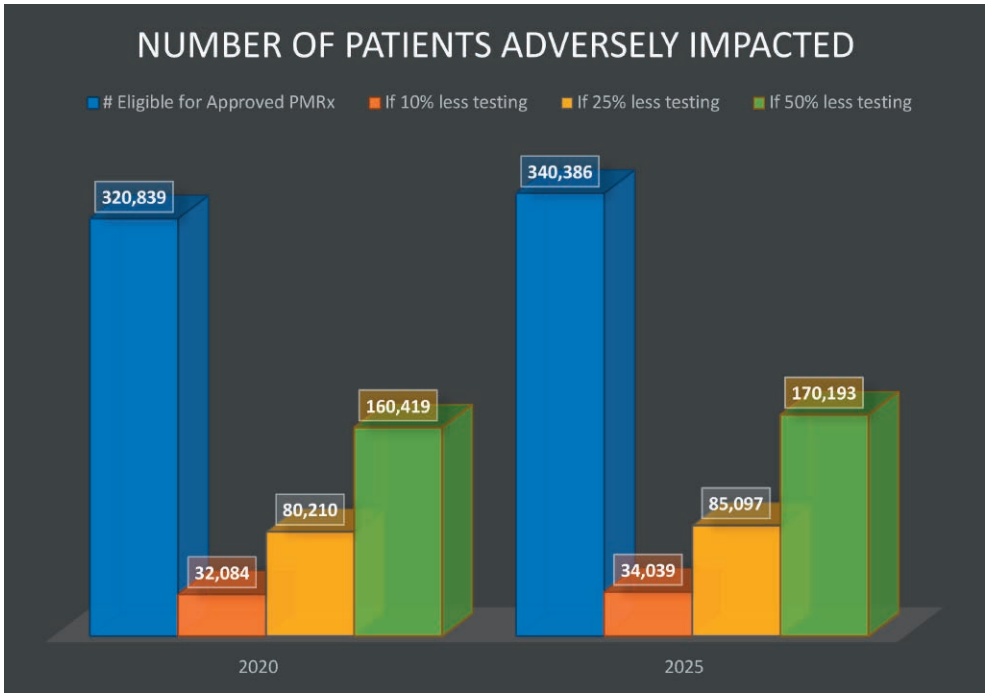

Figure 4: Case Study of IVDR impact on CDx testing for oncology patients eligible for an approved precision medicine (PMRx), assuming different modelling impacts (10%, 25%, 50%)

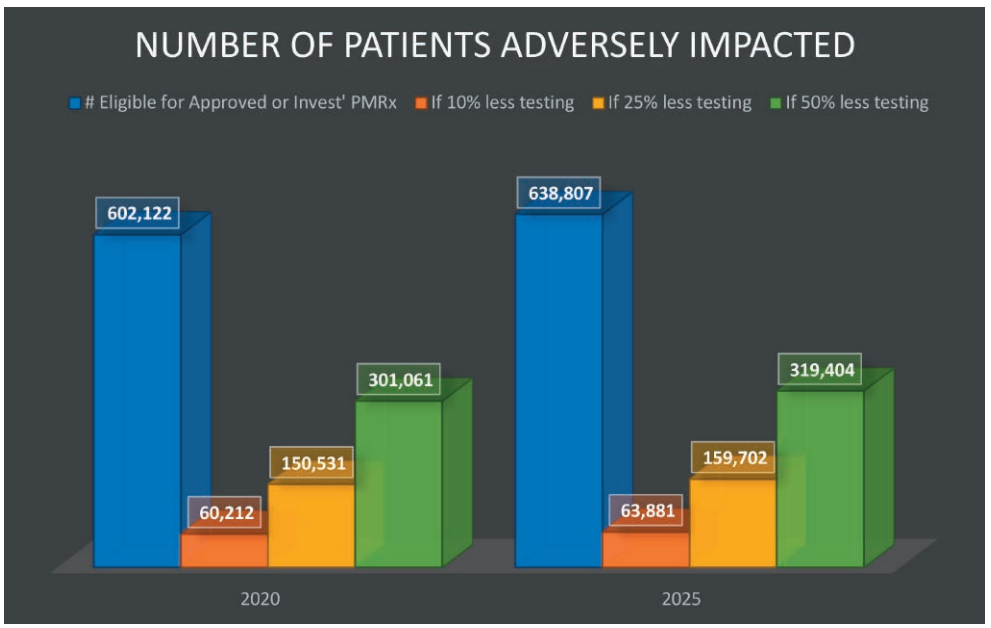

Figure 5: Case Study of IVDR impact on CDx testing for oncology patients eligible for an approved or investigational precision medicine (PMRx), assuming different modelling impacts (10%, 25%, 50%).

(**Figure 4**). These patients would therefore revert to less effective standard of care therapies with a consequent impact on life year improvements. With the rise in innovations and development of novel precision medicines, access to investigational PMRx would also be potentially affected that translates to an additional 6.4% of all new cancer patients diagnosed impacted (total impact 13.7%).[19] Maintaining the same conservative 10% lack of access to testing, this would impact almost twice the number of patients, with over 60,000 of these losing access to targeted therapies based on 2020 figures, rising to almost 64,000 in 2025 (**Figure 5**).

While this is a simplistic estimate of the potential impact to precision medicine patients that comprise only a small subset of the European patient community, it serves to illustrate the scale of the problem and the risk of real and severe life-changing consequences for the EU patient population if IVDR is applied as planned. Should the impact be greater than 10% then the issue becomes more serious with a greater impact to patient life years, quality of life for afflicted patients and overall healthcare cost. The consequences of modelling higher impacts (25% and 50%) are also illustrated in **Figures 4 and 5**. In our modelled worst-case scenario where 50% of patients cannot access testing required for prescription of approved or investigational PMRx, the situation escalates to impacting over 600,000 precision medicine patients, a situation that would have dire consequences for oncology outcomes in Europe.

For In-House Tests – Laboratory Developed Tests

CE-marked CDx devices can take the form of kits distributed for use at the customer site, or they can be single-site tests where patient samples are sent directly to an approved facility for testing and analysis. Such single-site facilities, however, should not be confused with *in-house developed tests* and run by healthcare institutions. In-house developed biomarker tests are widely employed across Europe to provide high-quality diagnostic testing that is a core component for the prescription of precision medicines. A recent case study at a large university hospital laboratory in Belgium showed that 47% of all the tests used for precision medicine treatment decision making are in-house tests.[20] In specialized laboratories, this number is around 80%.[9] Furthermore, a recently published report from Diaceutics was in broad agreement with these figures for in-house tests reinforcing the reliance of clinical communities on these tests for routine use with oncology precision medicines.[21]

The IVDR handles in-house tests differently from CDx devices. They are exempt from the requirements of the Regulation (apart from the general safety and performance requirements set out in Annex I), provided they meet the in-house device health institution exemptions outlined in Article 5(5) and described in **Table 2**. SHIs must meet the exemptions, or these tests must come out of service. It is reasonable to speculate that this will place limitations on the use of a sizeable proportion of these tests currently in service in health institutions across the Union, especially biomarker tests utilized for personalized healthcare decision making. This decrease will be driven largely by the fact that it will be challenging for SHIs to justify that there is no equivalent device already available on the market or that the marketed device cannot meet the SHIs' needs at the appropriate level of performance when a CDx device has been approved for use as a CE-IVD.

While quality testing and patient outcome is paramount, IVDR compliance also has major cost and resource implications for single healthcare institutions, many of which routinely run hundreds of independent in-house tests. In one case study,

Vermeersch *et al* reported that a major investment of time and effort would be required to bring all 537 in-house tests employed at their hospital to IVDR compliance.[20]

Compliance requires SHIs to allocate resources to evaluate their existing in-house device portfolio, prioritize which assays should be kept in service and ensure that all of the relevant general safety and performance requirements are met for each one. If an equivalent CE-IVD is available, then significant time, costs and resources are required to purchase the specified equipment and provide the necessary training to clinical scientists. Therefore, maintaining compliance with the IVDR will have to be planned into the budget of these Member States where most of them have nationalized health services and the costs must be defrayed by the exchequer.

Yet another unintentional consequence of these restrictions on the use of in-house tests and the associated costs of compliance with the new regulation for health institutions could be reduced access for patients to precision medicines, particularly in oncology (**Figure 6**).

Case Study – In-House Tests

A recent case study evaluating the impact of IVDR on the availability of in-house developed biomarker tests routinely used in clinical practice for personalized medicine delivery in non-small cell lung cancer (NSCLC) estimated that there is potential for a 25% reduction in in-house testing capacity in the first year following the IVDR date of application. Consequently, **over 40,000** NSCLC patients with actionable genetic alterations affected by these restrictions may not receive appropriate therapy in that year alone.[21]

Figure 6: Case Study of IVDR impact on in-house biomarker testing for oncology patients requiring personalized therapy

Conclusion

The healthcare community is clearly facing major challenges in implementing IVDR with the likelihood that thousands of IVDs will go off market and certification of new products will be significantly delayed, stifling innovation and impacting patient care. The case studies presented in this report consider only CDx and in-house tests for precision medicine patients. If we extrapolate to the wider EU patient population and conservatively estimate that even 10% of the 34,000 CE-marked IVDs requiring notified body assessment are not re-certified by the date of application, we are at risk of adversely impacting many thousands of European patients while the industry works to build the regulatory framework required for successful implementation. That is not even counting the routinely used laboratory developed tests by the health institutions. Earlier this year the Medical Device Coordination Group (MDCG) published an implementation plan for IVDR in which they outlined their planned tasks and priority actions.[22] Industry stakeholders including medical device manufacturers and trade associations, and even members of the European Parliament [personal communication with MedTech Europe], have called for further action and have proposed various solutions including postponement of the Regulation, extension of the grace period from high-risk to all device classes, and other transitional measures.[23,24,25] A similar tactic was taken for the MDR wherein implementation was delayed by one year as the industry was battling with the challenges of Brexit and the coronavirus pandemic. Based on our analyses, we predict that a simple one-year postponement of IVDR will not be adequate to ensure the continued management of patients. Therefore, there may be a need to consider other more pragmatic solutions to resolve the impasse for a smooth and successful transition to IVDR to minimize impact to patients, such as those outlined in **Figure 7**.

"The IVDR will improve the quality of diagnostic testing across the EU and its implementation is highly welcome."

Phased Implementation

1. Delay the IVDR date of application for 1-year post establishment of sufficient notified body capacity to ensure expeditious review and certification of the current IVDD portfolio and new product portfolio. This timeframe will allow:
    a. establishment of sufficient new notified bodies to be certified to meet demand
    b. to ensure notified bodies have sufficient hands-on experience of IVD review and certification activities (~1 additional year after their certification)
    c. to ensure all stakeholders are sufficiently versed with the requirements of the process to ensure success
2. Implement a phased review of IVDD re-certifications and new products (including new changes to existing products which require assessment) starting with Class B for a period of a further 1 year. Provide a grace period of a further 2 years for all Class C and Class D products.
3. Provide a grace period of 4 years (until May 2026 at the soonest) to Single Healthcare Institutions (SHI) to ensure a pragmatic transition to compliance of SHI to IVDR without adversely impacting patient access to critical healthcare testing.

Figure 7: Potential solutions for successful IVDR implementation

Exploring discretionary enforcement options

Derogation (extensions or exemptions) from conformity assessment procedures is an option in exceptional cases relating to public health or patient safety in accordance with IVDR Article 54.[7] For example, CDx tests are required to prescribe medicinal products in accordance with the Summary of Product Characteristics (SmPC). If the patient has no access to the required CDx then this could seriously affect their health. Such cases may be grounds for derogation, in which case the device manufacturer is required to make an application with respect to a specific IVD to a specific Member State. It is possible for the EC to then apply derogation across the EU, but it requires the European Commission to take action; a manufacturer could request that the Commission does this, but the Commission does not have a duty to consider the request. Moreover, requests for derogation for groups of devices or device types within Member States or across the Union is not possible.

Outlook

The IVDR will improve the quality of diagnostic testing across the EU and its implementation is highly welcome. Although the regulatory framework and guidance are still a work in progress, key stakeholders including device manufacturers, health institutions, notified bodies, competent authorities and pharmaceutical companies are underequipped and underprepared for this transition. As such it is necessary to ensure that the required infrastructure is in place ahead of implementation in order to ensure a seamless and productive transition. JoPM

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Ciara Airey

Ciara Airey has over a decade of experience in the IVD industry within R&D and regulatory affairs. Her industrial experience started at QIAGEN in the development and regulation of companion diagnostic assays, after which she moved into regulatory consulting and writing for the CRO, NAMSA, focusing primarily on IVDR compliance. Ciara recently joined GlaxoSmithKline as Associate Director of Regulatory Affairs where she continues to work in the area of clinical trials for precision medicines. Ciara holds a PhD and Research Masters Degree in Molecular and Cellular Biology, a postgraduate Diploma in Statistics and a Bachelor's Degree with Honors in Human Genetics.

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Maria Orr is currently Head of Precision Medicine for Biopharmaceuticals in AstraZeneca. In this role she leads the delivery of precision medicines and their associated companion diagnostics for drugs across a diverse range of therapeutic areas including cardiovascular, renal, metabolism (CVRM), respiratory and immunology (R&I), microbial science and neuroscience. Maria has extensive experience in the field of precision medicine and companion diagnostic development. With over 20 years' experience in the pharmaceutical industry, she has contributed to the successful launch of three personalised treatments in oncology and the delivery of over 30 companion diagnostic assays to the market to date.

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