In Vitro Diagnostic Regulation:
what it means for clinical flow cytometry labs

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The IVD industry is evolving as new technologies and approaches come on board. The IVDR's new rules and regulations have been created to meet these changes, and to create a robust, transparent and sustainable regulatory framework. This will ensure that IVD products and services meet the highest achievable levels of safety and efficacy, including Laboratory Developed Tests which are in the scope of the new regulation. Companies developing and supplying IVDs can help laboratories to navigate the IVDR by providing clear guidance about the process, and by creating pipelines of new IVD products that meet the needs of end users.

There has been a five-year transition period, ending on May 26, 2022 to be compliant. It will replace the current EU IVD Directive, which dates from 1998 (Directive 98/79/EC). The new IVD-R requires that most products undergo a conformity assessment by a Notified Body in order to achieve the CE-mark.

Beckman Coulter Life Sciences continues to devote time and resources to ensure our existing CE portfolio remains compliant and meets the higher safety and performance requirements outlined in the new EU Regulation. We are committed to remain a market leader and the supplier of choice of CE-IVD reagents.

We plan to be ready to meet new IVDR requirements well in advance of May 26, 2022. More importantly, we will strive to support customers through their own compliance journey by continuing to provide high-quality CE-marked products, consultation, and follow-up support as needed.

IVDR will result in major changes to the EU healthcare industry. It will not, however, alter our commitment to providing world-class products and and service to all our current and future customers.

Warmest regards,

Mario Koksch

Beckman Coulter Life Sciences

INTRODUCTION

In vitro diagnostic devices (IVDs) play a vital role in healthcare and influence a great many therapeutic healthcare decisions. They are used to test samples of tissue and bodily fluid to detect or rule out diseases, identify markers such as blood groups, make decisions about prevention or the best course of treatment, and track the development or improvement of illness over time. IVDs can be used in laboratories, at point-of-care in clinics, or at home.

The IVDR definition of an in vitro diagnostic device

'In vitro diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:

(a) concerning a physiological or pathological process or state

(b) concerning congenital physical or mental impairments

(c) concerning the predisposition to a medical condition or a disease

(d) to determine the safety and compatibility with potential recipients

(e) to predict treatment response or reactions

(f) to define or monitor therapeutic measures.

Specimen receptacles shall also be deemed to be in vitro diagnostic medical devices.

Examples of in vitro diagnostic devices include pregnancy tests and blood glucose monitors.

Source: Regulation (EU) 2017/746[1]

Until recently in Europe, IVDs were regulated by the In Vitro Diagnostic Medical Devices Directive 98/79/EC (IVDD). The IVDD was published on 27 October 1998,[4] and became mandatory in December 2003.[5] Its aim was to ensure and harmonize the safety, quality and performance of IVDs across the European Economic Area (EEA), including the 27 (now 26) member states of the European Union (EU), and the members of the European Free trade Association (EFTA; Iceland, Liechtenstein and Norway).[5,6]

A lot has changed in the world of IVDs over the past two decades, with huge advances in technology, including next-generation sequencing moving from research to routine testing. There have also been issues related to safety and how the IVDD has been applied in different member states. These challenges all needed a new regulation to recognize technological change, reduce conflicting interpretations of the rules, and avoid future incidents concerning product performance.[7,8]

As a response, the In Vitro Diagnostic Regulation (EU) 2017/746 (IVDR)[1] was proposed in 2012, and the final text agreed in 2016. It was then published on 5 April 2017 and came into force on 25 May 2017. The IVDD will be repealed fully from 26 May 2022, and the IVDR will apply fully from this date.[1,2,7,9]

The aim of the IVDR is to ensure: [7,8]

- Harmonized application across the EU
- Tighter controls and a consistently high level of health and safety protection for EU citizens
- Free and fair trade of the products throughout the EU
- Reflection of recent scientific and technological progress
- Continued innovation
- Improved competitiveness.

As stated in the IVDR, the regulation's scope is that it: "lays down rules concerning the placing on the market, making available on the market or putting into service of in vitro diagnostic medical devices for human use and accessories for such devices in the Union. This Regulation also applies to performance studies concerning such in vitro diagnostic medical devices and accessories conducted in the Union."[1]

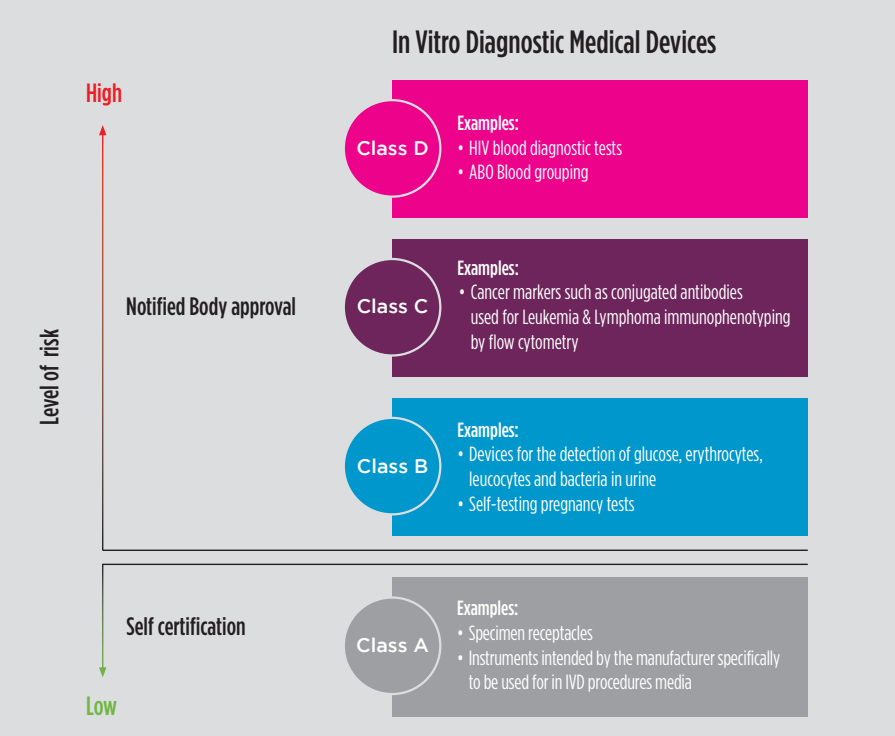
What is covered by the IVDR	What isn't covered by the IVDR
• In vitro diagnostic medical devices for human use and accessories for such devices ◆ This includes laboratory-developed tests (LDTs) • Performance studies concerning such in vitro diagnostic medical devices and accessories	• Products for general laboratory use or research-use only products, unless specifically intended to be used for in vitro diagnostic examination • Invasive sampling products or products which are directly applied to the human body for the purpose of obtaining a specimen • Internationally certified reference materials • Materials used for external quality assessment schemes

Source: Regulation (EU) 2017/746[1]

The IVDR will also include EUDAMED (European Database on Medical Devices), a comprehensive medical devices database that will track all medical devices on the market in the EU, and a new device identification system, based on a unique device identifier (UDI), that will improve the traceability of medical devices.[7]

Manufacturers need to show that their devices meet the requirements of the IVDR, by conducting a conformity assessment. The conformity assessment procedure will depend on the risk classification of the device (see Figure 1).

Figure 1: Risk-based classification of devices



Under the IVDR, tests are categorized according to the impact of the risk of failure. Class A covers tests where failure of a test could lead to a low individual risk and minimal public health risk, and these do not require the involvement of a notified body. Class B, which includes point-of-care and self-testing, involves moderate individual risk and/or low risk to public health. In classes C and D, which cover most laboratory tests, failure could mean moderate to widespread risk to public health or high to life-threatening risk to individuals. Classes B to D require the involvement of a notified body, which is an independent organization designated by the National Competent Authority of a European Member State to assess the conformity of an IVD against the requirements of the IVDR..[1,4,10,11]

The changes with the IVDR will have a wide impact, from the companies developing the tests, through the every-day work of the clinical laboratories, and potentially to the physicians and patients. One of the biggest effects of the IVDR will be on laboratory-developed tests (LDTs), which are largely carried out in flow cytometry labs. These are tests that are developed in-house and used within a single clinical laboratory. LDTs were previously excluded from the IVDD but are in scope of IVDR.

Under the remit of the IVDR, and provided they meet the requirements of article 5.5 (see 'In practice'), clinical laboratories can continue to use LDTs (with additional documentation) if there are no equivalent CE-marked tests available. However, if the laboratory wants to continue using its LDTs to test samples from patients in Europe despite there being equivalent tests available, it will be deemed to be a manufacturer and have to comply with all of the requirements of the IVDR. This may require significant additional work for the laboratory.[12] Labs are responsible for meeting their obligations under article 5.5 if they want to continue doing home brews. Labs are responsible for meeting their obligations under article 5.5 if they want to continue doing home brews. Manufacturers are not responsible to support them in this effort. Manufacturers may have an interest in proposing already CE-marked tests to meet laboratory needs so that they avoid the burden of having to meet article 5.5.

REGULATORY IMPACT

A lot has changed in the world of in vitro diagnostics since the beginning of the IVDD in 1998. It was inevitable that there would need to be new regulations put in place to meet the needs of the IVD market now and into the future. Many of the new requirements of the IVDR are extensions of those of the IVDD, expanded to come in line with more stringent regulations elsewhere in the world.

The key changes in the IVDR include:[9,13,14]

- Inclusion of LDTs
- Re-classification of IVDs according to risk
- Implementation of unique device identification
- Additional data required to demonstrate product performances and stability
- More post-market surveillance, with greater involvement from notified bodies
- Stricter requirements for technical documentation and clinical evidence
- Stricter requirements for economic operators
- Requirement for someone in the manufacturing company to have a formal responsibility for overseeing regulatory compliance.

Classification and UDIs

The IVDD classified IVDs into two lists, which determined the need for a notified body to be involved in certification (Table 1). The lists, which are in Annex II of the IVDD, are broadly risk-based (see the appendix for further details).

Table 1: IVDD classification

Category	Notified body?	Example
Annex II List A (high risk)	Yes	HIV, hepatitis, blood grouping
Annex II, list B (lower risk)	Yes	Rubella, prostate-specific antigen, blood glucose self-testing
Self-test (tests carried out by the patient)	Yes	Pregnancy, cholesterol home tests
General (all those not covered by List A or B, or by the self-testing group)	No	Tests for hormones, cardiac markers, clinical chemistry

Source: EU4; BSI[11,5]

Classification in the IVDR has moved from a list-based approach to a risk-based approach.

Table 2: IVDR classification

Class	Notified body?	Risk	Example
A	No	Failure of a test could lead to a low individual risk and minimal public health risk	Specimen receptacles Instruments specifically for IVD procedures
B	Yes	Moderate individual risk and/or low risk to public health	Tests run in clinical laboratories Near-patient testing in health institutions Self-testing for pregnancy, fertility, cholesterol level, or for glucose, erythrocytes, leucocytes, and bacteria in urine
C		Failure of a test could lead to a moderate risk to public health or a high risk to an individual	Self-testing for other markers Blood grouping or tissue typing prior to transfusion or transplant (depending on markers) Detecting infectious agents without a high risk of propagation Companion diagnostics
D		Failure of a test could lead to a widespread threat to public health or a life-threatening risk to an individual	Detection of transmissible agents that cause a life-threatening disease Measuring infectious load where it is critical for patient management Blood grouping or tissue typing prior to transfusion or transplant (depending on markers)

Source: EU[1]; BSI[11], EU IVDR Wiki[10]

While both the IVDD and the IVDR aim to eliminate or reduce risk, the IVDR has an additional requirement for manufacturers to establish, document, implement and maintain a system for risk management, as well as have a risk management plan for each product.

Under the terms of the IVDR,[4] risk management is a constant and iterative process that requires updating throughout the lifecycle of the device. The risk management plan for each device includes:

- Identifying known and foreseeable hazards
- Estimating and eliminating/controlling the risks during intended use and reasonably foreseeable misuse
- Evaluating the impact of post-market surveillance information on risks and hazards
- Amending control measures as required

By carrying out this risk management process, manufacturers can support their customers, and reduce the risks involved in using the IVDs.

Under the IVDR, all IVDs on the market in Europe will need to carry a UDI. This brings Europe into line with the US, where the Food and Drug Administration (FDA) has required UDIs since 2013. UDIs are barcodes that link to information in a database for use by manufacturers, laboratories and regulators, as detailed in Annex VI, part B of the IVDR (see appendix).[1,4,10,15]

The deadline for UDI labelling is:[10]

- Class D devices from 26 May 2023
- Class C and B devices from 26 May 2025
- Class A devices from 26 May 2027.

The role of the notified body

Under the IVDR, notified bodies will need to be involved in the certification of IVDs that have a risk classification of B, C or D.[13] Notified bodies are independent certification organizations. They are assigned the role ('notified') by the competent authority in a member state to be able to determine whether an IVD can be CE marked.[1,4,10]

Notified body: definition from the IVDR[1]

- 'conformity assessment body' means a body that performs third-party conformity assessment activities including calibration, testing, certification, and inspection
- 'notified body' means a conformity assessment body designated in accordance with this Regulation

All IVDD notified bodies will be rendered void on 26 May 2022, but many are likely to remain under the IVDR. As of September 2020, there were four notified bodies in place in the EU, with others waiting for designation (Table 3).

Table 3: EU Notified Bodies designated under the EU IVDR (2017/746)

BSI Group The Netherlands B.V.
DEKRA Certification GmbH
TÜV Rheinland LGA Products GmbH
TÜV SÜD Product Service GmbH Zertifizierstellen

Correct as of 6 September 2020
Source: Nando database[16]

Whereas notified bodies focused more closely on analytical performance under the IVDD, they now have responsibility for looking into a test's scientific validity (link between analytical and clinical performance) and carrying out performance evaluations. Samples of their assessments of a manufacturer's technical documentation will be routinely reviewed by competent authorities, as will all conformity assessment reports for class D devices.[10]

Performance and surveillance

The IVDR covers product performance from cradle to grave, including tracking the IVD's performance and monitoring how it performs compared with other products. The IVDD required a pre-market performance evaluation, which was focused on the IVDs' analytical performance. The IVDR's pre-market performance evaluation requires collation of data on the device's scientific validity, clinical performance, and clinical evidence (including analytical performance), and this must be assessed and presented in a performance evaluation report.

Following launch, the IVDR requires post-market performance follow-up, and the manufacturer must have a post-market performance follow-up plan. This plan will include a continuing review of the performance evaluation report, ensuring that it reflects current research and the ongoing status of the device. This forms the basis for the post-market performance follow-up evaluation report.[1,4,10]

The IVDD did not specifically mention post-market surveillance (PMS), but required manufacturers to maintain "systematic procedure to review experience gained from devices in the post-production phase". The IVDR has made this clearer by including a definition of post-market surveillance.

Post-market surveillance: definition from the IVDR[1]

'Post-market surveillance' means all activities carried out by manufacturers in cooperation with other economic operators to institute and keep up-to-date a systematic procedure to proactively collect and review experience gained from devices they place on the market, make available on the market or put into service for the purpose of identifying any need to immediately apply any necessary corrective or preventive actions

The post-market surveillance system needs to gather, record, and analyze data in order to:

(a) update benefit-risk determination and improve risk management

(b) update design and manufacturing information, instructions for use and labelling

(c) update performance evaluation

(d) update the summary of safety and performance

(e) identify needs for preventive, corrective or field safety corrective action

(f) identify options to improve usability, performance, and safety

(g) contribute to post-market surveillance of other devices (where relevant)

(h) detect and report any trends in incidents.

This data is then used to create a PMS report. For devices in classes A and B, this report needs to be kept available for competent authorities. For devices in classes C and D, the higher risk classes, a periodic safety update report (PSUR) needs to be produced. This includes benefit-risk evaluations and post-market performance follow-up findings, and must be updated annually. For class D devices, the PSUR must be submitted annually to

the notified body, and made available to the competent authorities via EUDAMED, the IT system created by the European Commission to implement the Medical Device Regulation (MDR) and the IVDR.[1,4,10]

The amount of data collected is one of the biggest changes between the IVDD and IVDR. The data to be collected under the IVDR includes: [1,4,10]

- UDI
- Manufacturer
- Authorized representative
- Importer
- Distributor
- Notified bodies and certificates
- Performance studies
- Vigilance
- Post-surveillance data.

The vigilance requirements in the IVDD were limited. The IVDR separates out vigilance and post-market surveillance, and expands the needs for vigilance (identification, reporting and trending of serious incidents) compared with the IVDD. The IVDR adds in a 15-day reporting deadline for reporting serious incidents other than death or serious health deterioration, as well as reporting significant increases in the frequency or severity of incidents. Vigilance reports need to be submitted to a central database rather than to the national competent authority.[1,4,10]

New stakeholders

The IVDR also covers new stakeholders. A lot of devices come from outside of the EU, so the authorized representative in the EU has a critical role. The authorized representative must be established in the EU and have a written mandate from the manufacturer outside the EU to act on the manufacturer's behalf. Responsibilities include verifying that the declaration of conformity and technical documentation has been completed, and that a conformity assessment has been carried out if required. The authorized representative also has to ensure that copies of documentation are available to authorities, and that the required documentation is recorded in EUDAMED. Authorized representatives are liable for defective devices placed on the market along with the manufacturer.[13]

Importers who place devices from a third country onto the market in the EU must be established in the EU. They need to ensure that devices are CE-marked, have the correct labelling and documentation, have a UDI if required, and are registered on EUDAMED. Distributors are people, other than manufacturers or importers, that put devices in the supply chain. Distributors need to be sure that the devices are CE-marked, that they have a declaration of conformity, and that labels and instructions for use are in the correct European languages. The importer's name should be on all devices or accompanying documentation, and the importer should ensure that devices have a UDI. Manufacturers and authorized representatives will also need a PRRC.

The IVDR timeline

The beginnings of the IVDR can be traced back to 2010, when the European Commission consulted on the revision of the IVDD. This directive had been introduced in 1998 and become mandatory in December 2003.5 As a directive, it laid down what it needed to achieve, but it was up to each member state to decide how these should be transposed into national laws. Because of this, the IVDD could potentially be interpreted and applied differently across the EU. IVD technology had also changed substantially since 1998, and so the classifications of devices had become outdated. Issues with medical devices that put patients at risk also meant that there was a need for better patient protection.

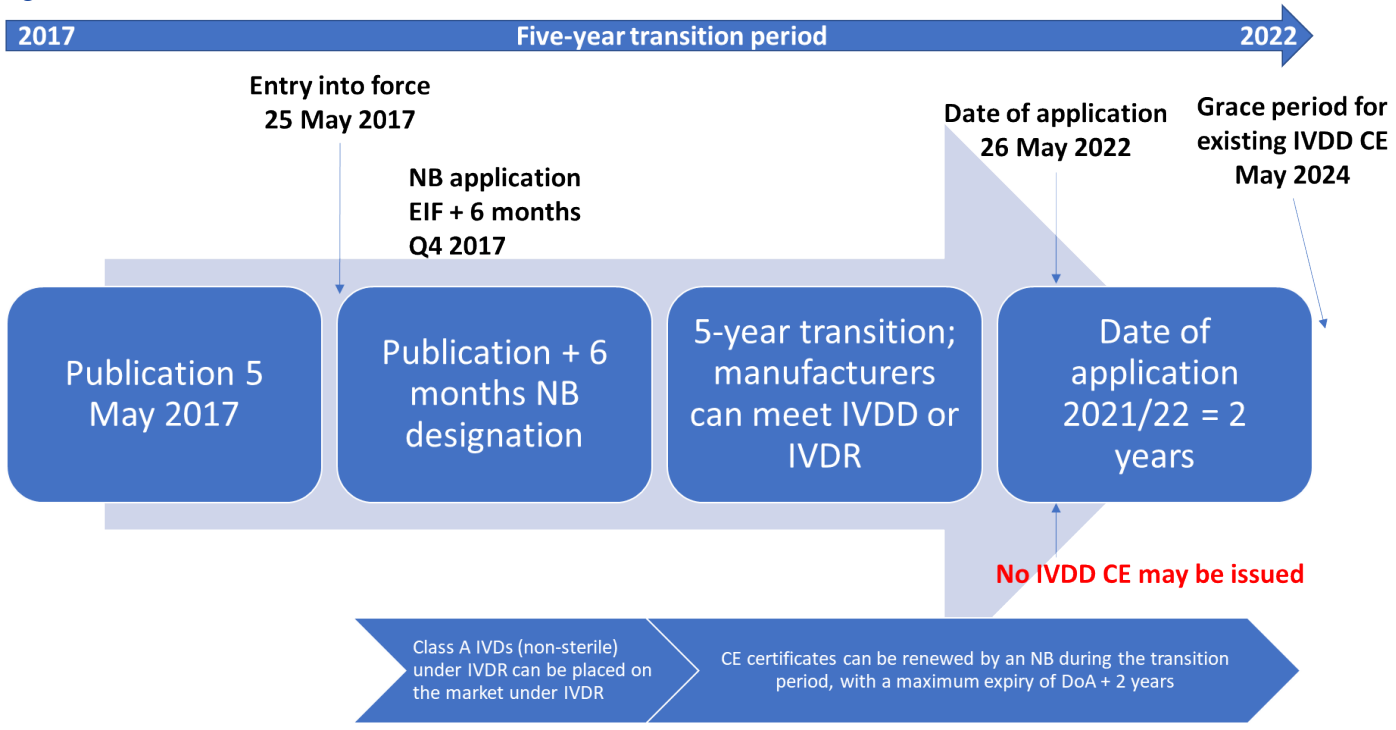
After its consultation, the Commission proposed a replacement for the IVDD, in the form of a regulation, in 2012. As a regulation, the IVDR would be legally binding throughout all member states.

There were a number of steps to the implementation of the IVDR:[1,7,13,14]

- 5 October 2015 – EU ministers agreed a general approach to medical devices
- 15 June 2016 – European Parliament and Council agreed the final text
- 7 March 2017 – Council voted its first reading position
- 5 April 2017 – adopted without modification by the European Parliament

The IVDR came into force on 25 May 2017 with a five-year transition period, which ends on 26 May 2022 (date of application). The IVDD will be repealed fully from 26 May 2022, and the IVDR will apply fully from this date (see Figure 2).[1,2,7,9]

Figure 2: IVDR timeline



Source: Adapted from Conway (BSI)[14]

The aim of the transition period was to avoid any delays or disruptions in the supply of medical devices. During the transition period, devices that are compliant with either the IVDD or the IVDR can be put on the market.

Products placed on the market under the IVDD will be exempt from clinical investigation requirements, provided:

- Their clinical evaluation is based on enough data
- They comply with relevant common specifications.

Certificates issued by notified bodies under the IVDD become void at date of expiry, or by 27 May 2024 at the latest. Products CE-marked under the IVDD that were placed on the European market prior to the IVDR's date of application (May 26 2022), can continue to be made available or put into service until May 27 2025.[9]

There are a number of Delegated Acts and Implementing Acts that are required to supplement and adapt the IVDR to ensure it works properly. These include: [13,14]

- Regulatory status of groups of products
- Common Specifications
- Format of Summary of Safety and Performance (SSP)
- UDI
- EUDAMED
- List of Notified Body Operations Group (NBOG) codes
- NB designation procedure.

The implementation of the IVDR, and the additional requirements over and above those of the IVDR, will have practical implications for companies manufacturing IVDs and the related reagents and equipment, and on the laboratories that are carrying out the tests. There is also potential for a knock-on effect for physicians and their patients.

IN PRACTICE

As the IVDR is put into practice, the biggest impact for manufacturers will be the need for certification from notified bodies for the vast majority of IVDs, and the requirement for more detailed documentation and analysis throughout the entire product lifecycle. Previously, around 7% of IVDs under the IVDD needed the involvement of a notified body; this has now risen to around 84%.[17]

So far, only a limited number of notified bodies have been designated by the EU (see Table 3), and some national regulatory agencies have not fully prepared for the arrival of the new tests. While the numbers of both designated notified bodies and fully prepared national authorities will increase, there is potential for a bottleneck once the IVDR is fully in place. This could result in delays for CE marking of new tests, or risk existing tests having to be taken off the market temporarily while recertification takes place. Ultimately it could result in shortage and interruption of medical devices and IVD supply to the European market.

The fees payable to a notified body for an initial certification cycle will vary according to the class of the IVD and the number of IVDs within each class. This process is likely to include an initial audit and surveillance audits, as well as documentation reviews for the entire range of IVDs. The notified body will also carry out routine certification cycles for recertification and ongoing surveillance, for as long as certification remains in place.[18] This will increase the costs for the manufacturer for both initial certification and ongoing surveillance, as well as increase the time required to prepare for certification and audit.

The need for more data and documentation

For new products, manufacturers will have to carry out more studies on their products to create the data required to back up the device's scientific validity, clinical performance, and clinical and analytical performance. For products that are manufactured before May 2022, manufacturers will be able to maintain existing IVDD certification until 2024. For any new lots of existing products manufactured after May 2022, IVDR certification will need to be put into place (except products which were certified by a notified body under the IVDD, which can continue to be manufactured and placed on the market until May 26 2024 or until expiration of the IVDD CE certificate). This will require manufacturers to assess their historical data and carry out a lot of remediation work, such as conducting literature searches to find published reports or even performing new studies on old products if the data is not sufficiently robust. These assessments, and any additional studies, will need to be carried out by qualified people, so manufacturers may need to take on more staff. Processes will also need to be put into place to ensure that the data and documentation are kept up to date throughout the product lifecycle.

Another new requirement that will increase staffing costs is the need for a person (or persons) responsible for regulatory compliance (PRRC). The role is mandatory for manufacturers and authorized representatives,, and should be a full-time role for a large company. Micro- and small enterprises can contract this role out, but must have someone who is always accessible.

Manufacturers will need to upgrade their existing quality management systems to meet the needs of the IVDR, and to handle the increased numbers of products that will have to be tracked. The system will also have to be robust enough to meet needs going forwards.

Putting together the reports required by the IVDR for both existing and new products, and carrying out surveillance post-market, could potentially extend the time taken to license a new product, delaying the point at which the manufacturer will start to get a return on its investment.

All of these changes will increase the cost and the complexity of test development and approval. Smaller companies will be put at a disadvantage, and may even be forced to close, as they will not have the economies of scale that larger companies can exploit. The increased costs could also lead some companies to divest or stop production of IVDs or reagents with smaller markets, as they will need to balance the cost of the changes required for each product with the economic return. This may have a disproportionate impact on less-used tests, such as those for orphan diseases or rare infections and cancers. On the other hand, the changes could provide opportunities for IVD manufacturers that wish to specialize in a broader range of lesser-used tests.

The impact on laboratory-developed tests

One of the areas where the IVDR will have a major impact is on laboratory-developed tests (LDTs), also known as 'home brew tests'.

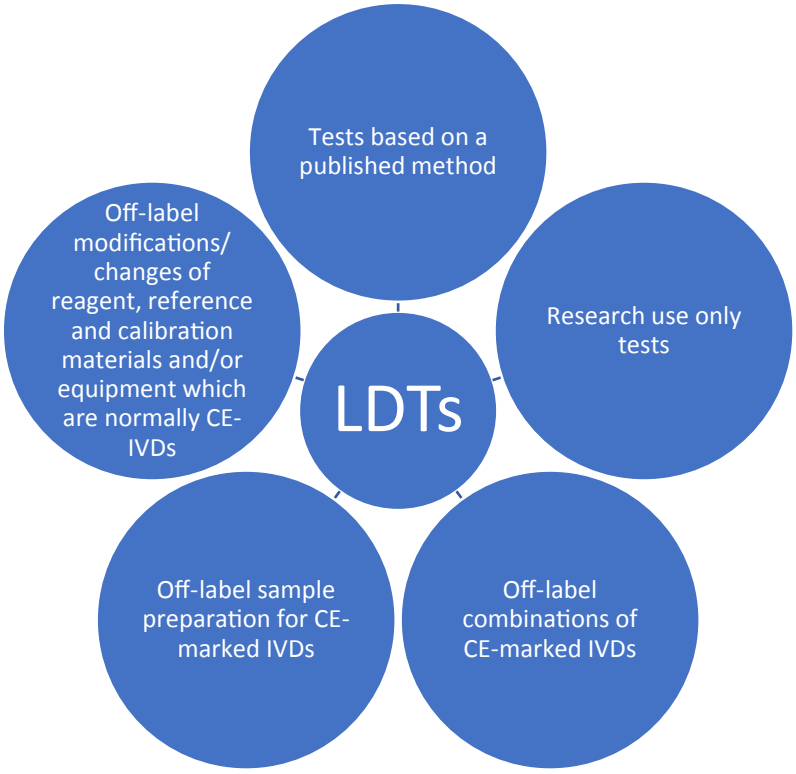
LDTs are created for use in a single laboratory. They are often developed when there isn't a suitable IVD test to meet a specific analytical or clinical need, for example:[17,19]

- Identifying a rare disease where there are no tests available
- Diagnosing and finding treatments for infectious diseases that are rapidly evolving, or where there is a risk of antimicrobial resistance
- Identifying mutations to find supplementary therapeutic options
- Characterization of genetic mutations found in inheritable disorders
- Genomics where the science is still emerging
- Flow cytometry where laboratories must combine multiple conjugated antibodies to diagnose and monitor pathologies based on the expression level of multiple markers

LDTs may also be developed when a lab doesn't have the budget or the space for additional laboratory equipment, so use equipment and reagents from different vendors, or research-only reagents. They may be adapted from existing tests to increase the variety or performance (see Figure 3).[17,19]

LDTs may be simple and test for a single analyte such as sodium, or be complex and test for an array of DNA variations for the diagnosis of a genetic disorder.[20] They are especially important for diagnosing emerging diseases, and have played a major role in the Covid-19 outbreak that began in late 2019.[17]

Figure 3: Different types of LDTs



Source: Vermeersch17

When the IVDD was originally put in place, there was feedback, particularly from microbiology and other laboratories in the UK that created and used their own tests, reagents, and media. This led the EU to grant an exception for making own 'home brew' products for microbiology and clinical chemistry.

The IVDR has taken a different approach, and has included LDTs as a test that requires regulation. Using LDTs in the absence of the controls and tests required for CE-marked IVDs places a lot of responsibility on the laboratory and its staff. The results from LDTs are used by physicians to diagnose their patients, or to make decisions on their treatment. If the result of an LDT is wrong, patients could be diagnosed incorrectly, or be over-treated, under-treated or given the wrong drugs entirely. Any of these could be life-changing or life-threatening.

A device may be placed on the market or put into service only if it complies with this Regulation when duly supplied and properly installed, maintained and used in accordance with its intended purpose[1]

IVDR article 5.1[1]

Devices that are manufactured and used within health institutions, with the exception of devices for performance studies, shall be considered as having been put into service[1]

IVDR article 5.4[1]

With the exception of the relevant general safety and performance requirements set out in Annex I, the requirements of this Regulation shall not apply to devices manufactured and used only within health institutions established in the Union, provided that all of the following conditions are met:

(a) the devices are not transferred to another legal entity;

(b) manufacture and use of the devices occur under appropriate quality management systems;

(c) the laboratory of the health institution is compliant with standard EN ISO 15189 or where applicable national provisions, including national provisions regarding accreditation;

(d) the health institution justifies in its documentation that the target patient group's specific needs cannot be met, or cannot be met at the appropriate level of performance by an equivalent device available on the market;

(e) the health institution provides information upon request on the use of such devices to its competent authority, which shall include a justification of their manufacturing, modification, and use;

(f) the health institution draws up a declaration which it shall make publicly available, including:

(i) the name and address of the manufacturing health institution,

(ii) the details necessary to identify the devices,

(iii) a declaration that the devices meet the general safety and performance requirements set out in Annex I to this Regulation and, where applicable, information on which requirements are not fully met with a reasoned justification therefore

IVDR article 5.5[1]

Using any IVD requires confidence in the test's analytical performance (performing as intended), clinical performance (measurement of presence, absence or risk of disease and scientific validity).[19] The aim of the inclusion of LDTs into the IVDR is for them to have the same oversight as those available commercially, helping to ensure patients are protected from unsafe tests and doctors can rely on the results when they make treatment decisions.

Under article 5 of the IVDR, if there is an equivalent CE-marked test available to be bought 'off the shelf', the LDT will be treated as a test 'put into service' and will come under the full constraints of the IVDR, as with any

Preamble 29

Health institutions should have the possibility of manufacturing, modifying and using devices in-house and thereby addressing, on a non-industrial scale, the specific needs of target patient groups which cannot be met at the appropriate level of performance by an equivalent device available on the market. In that context, it is appropriate to provide that certain rules of this Regulation, as regards devices manufactured and used only within health institutions, including hospitals as well as institutions, such as laboratories and public health institutes that support the health care system and/or address patient needs, but which do not treat or care for patients directly, should not apply, since the aims of this Regulation would still be met in a proportionate manner. It should be noted that the concept of 'health institution' does not cover establishments primarily claiming to pursue health interests or healthy lifestyles, such as gyms, spas, wellness, and fitness centers. As a result, the exemption applicable to health institutions does not apply to such establishments.

other manufacturers' IVD. This means that a healthcare institution that develops and uses an LDT where there is a CE-marked alternative available will effectively be a manufacturer.

If there is no equivalent test for the specific needs of a patient group that has the appropriate level of performance,[17] a laboratory may continue to use an LDT, as described under Preamble 29, provided it meets the requirements of article 5.5.

Despite the fact that LDTs are often significantly cheaper than CE-marked IVDs, cost cannot be used as a justification; the only justification is where the needs of patients cannot be met at an appropriate level of performance. With some tests this justification may be challenging.

While a laboratory using such an LDT will be exempt from the IVDR requirements as a manufacturer, it must draft justifications (including clinical justifications) for using the LDT rather than a CE-marked IVD. It will have to comply with the relevant sections of the IVDR's Annex I General safety and Performance Requirements (GSPR), including monitoring and recording the performance of the test, and maintaining documentation about the test's manufacture and use. The laboratory will also have to justify why any omitted requirements are not applicable.[17,21]

The Annex I General safety and Performance Requirements are set out in three chapters: (I) general requirements; (II) requirements regarding performance, design, and manufacture; and (III) requirements regarding the information supplied with the device. The general requirements include aspects of health and safety, risk reduction and management, safe transport and storage, and considerations of benefit vs risk. The second chapter ensures that the design and manufacture take into account performance, construction, and protection of the patient. And the third chapter focuses on labeling and instructions for use.[21]

The 'orphan' LDT will also be subject to inspection from the national authority and will need to have a suitable quality system in place. Full certification from a notified body will not be required, as long as all of the requirements of article 5.5 are met.[17,21]

While the focus is on maintaining patient safety, increases in regulations that limit the development and use of LDTs could reduce innovation. They could also affect patient care by making it harder for laboratories to

modify existing diagnostics or create new ones that are tailored to the needs of a particular patient group or setting, or that are responding to an outbreak of an emerging disease.

Diagnostic management teams can rely on the expertise that arises from clinical laboratory medicine to help them reduce diagnostic errors and optimize clinical testing.[19] Increased regulations could reduce the skills base and expertise in clinical laboratories, moving it towards a service rather than an intrinsic part of the medical team.

The aim of the IVDR is to harmonize and improve the safety, quality, and performance of IVDs across Europe, thereby ensuring that patients are kept safe, and that physicians' diagnoses and treatment choices are as precise as possible. It is possible, however, that the IVDR could increase the cost of tests to laboratories, which will pass on these costs to often cash-strapped healthcare providers. Pressures on the system, particularly in the early years, could also slow the CE marking of existing and new devices.

Any delays to products coming to market, or interruptions to supplies of marketed IVDs, could mean delays to physicians getting access to diagnostics. This could push back diagnoses of life-threatening diseases, or patient access to treatment.

PROBLEMS AND SOLUTIONS

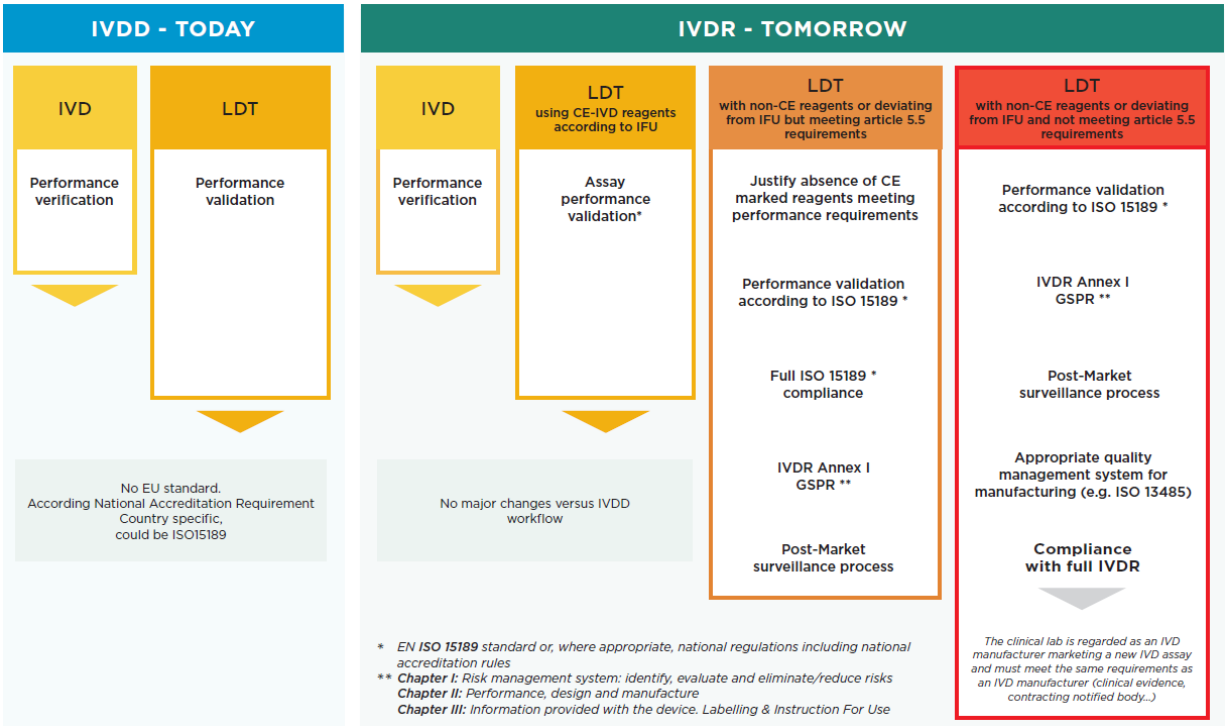
The biggest change, and in some cases the biggest challenge, faced under the new IVDR will be for laboratories that carry out LDTs. For these laboratories, article 5 of the IVDR will mean they need to stop using LDTs where there is a CE-marked alternative with the appropriate level of performance, or face having to be considered a manufacturer under the terms of the new regulation. For those that have LDTs they use because there is no CE-marked alternative, they will still need to put additional quality management processes in place, and face scrutiny from the national authority.[17,21]

This will have a disproportionate effect on flow cytometry laboratories that provide patient-related diagnostic information, as these are where many LDTs are carried out. The IVDR will make their day-to-day work more complex, and potentially more costly. Laboratories that are having to move away from LDTs, as they don't wish to be considered a manufacturer, will also need to make investments in specific equipment and reagents.

A clinical laboratory that wishes to develop and use LDTs where CE-marked alternatives are already available, must effectively align themselves with manufacturers and comply with the full IVDR.

The quality management system must be compliant with ISO-15189:2012 (Medical laboratories — Requirements for quality and competence),[22] or, where appropriate, national regulations including national accreditation rules, and must cover all diagnostic phases (pre-analytical, analytical and post-analytical). The laboratory needs to be accredited for each measurement and analysis. Figure 4 summarizes the differences between the LDT and IVD validation workflow under the IVDD and IVDR.

Figure 4: LDT vs IVD validation workflow



Source: Beckman Coulter

Accrediting flow cytometry tests is particularly challenging. Whereas hematology and clinical chemistry tend to use highly standardized tests based on automated and ready-to-use commercially available assays, flow cytometry panels are often LDTs and tend to be more complex. Flow cytometry tests are more likely to require assay development, manual sample preparation and complex data processing/analysis. Where they are used in diagnosis, such as for hematological malignancies, they are dependent on fast-moving science, with testing protocols constantly under review.

While laboratories should already be compliant with safety requirements in order to protect their patients, the standards bar for IVDR has been raised significantly higher. It will not be easy for a laboratory to comply with all the requirements required of a manufacturer. If a laboratory wishes to continue using LDTs when there is a CE-marked alternative available, it needs to look at the additional costs for staffing and documentation, and whether the outcome is worth the additional cost and effort. Being a manufacturer is not the core business of a laboratory. IVD companies benefit from economies of scale, as they can establish processes that cross the entire organization, but it is unlikely to be feasible for a laboratory that wants to do it for one product. Some issues also remain unclear: for example, is a big chain of laboratories across the EU classed as a single health institution?

For a laboratory looking to make its way through the transition from IVDD to IVDR, the first step is to make an inventory of all the tests that are carried out, and ask a number of questions:

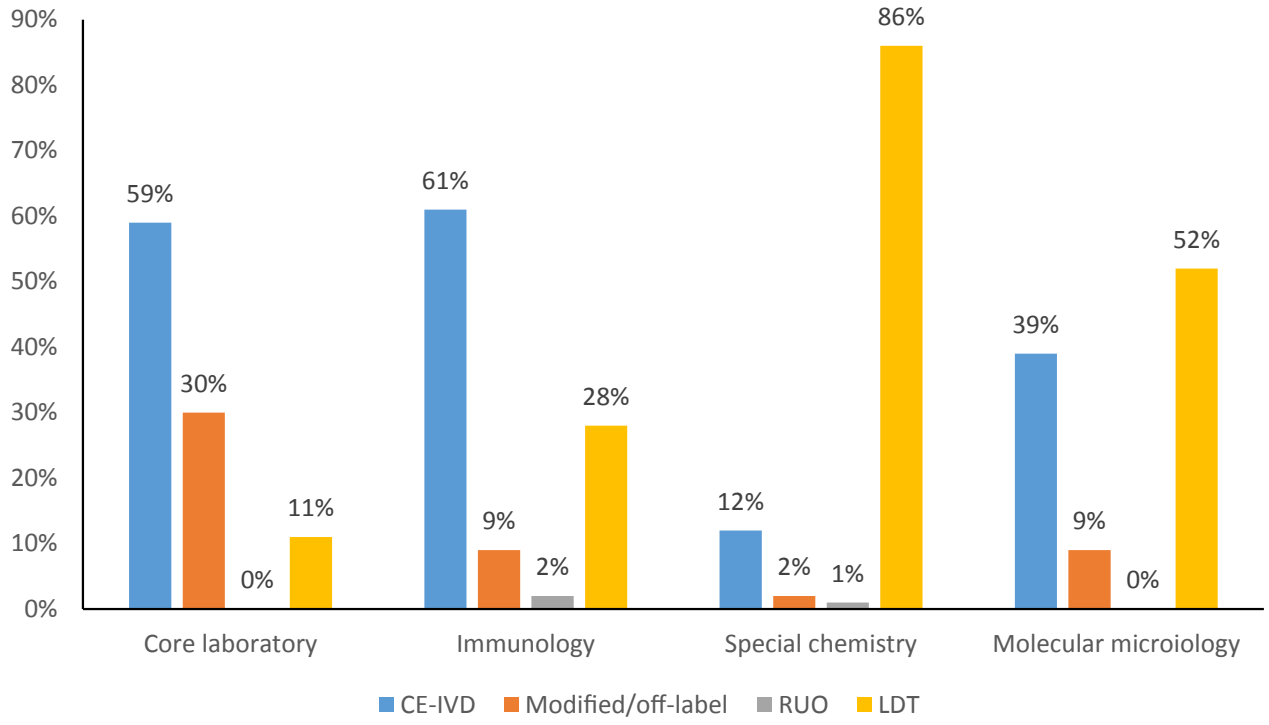
- Which tests carried out in the laboratory are CE-marked IVDs, modified IVDs or LDTs?
- Of the CE-marked IVDs, are any of them provided by small companies that don't seem to have put anything in place for the transition to IVDR?
- Which of the modified IVDs or LDTs can easily be swapped out with IVDR-compliant CE-marked IVDs?
- Are there one or more CE-marked IVD suppliers that can provide all or the majority of the tests carried out in the laboratory?
- Are there tests for where a rationale can be provided to continue with use of an LDT without being defined as a manufacturer?
- Can the laboratory be defined as a European health institution?
- Does the laboratory have sufficient resources and is the laboratory management team willing to take up the responsibility of all the requirements of the IVDR if they wish to continue LDTs where CE-marked alternatives are available?

Taking the first step

- Carry out audits of in-house tests, including CE-marked IVDs, modified IVDs and LDTs
- Reach out to all stakeholders (especially small ones) and find out what their plans are:
  - Manufacturers of tests, reagents, and equipment
  - Authorized representatives
  - Importers
  - Distributors
- Talk to notified bodies and regulators
- Reach out to stakeholders for help and support

In a recent case study,[17] researchers compiled a list of all laboratory tests carried out at the Clinical Department of Laboratory Medicine of the University Hospitals Leuven in May 2019, classifying each as a CE-IVD, modified/off-label CE-IVD, research use only (RUO) or LDT. The tests were also classified into core laboratory (e.g., automated chemistry and hematology analyzers), immunology (e.g., protein electrophoresis, autoimmunity testing, allergy), special chemistry (e.g., rare disease testing, mass spectrometry) and molecular microbiology testing (e.g., hepatitis C).

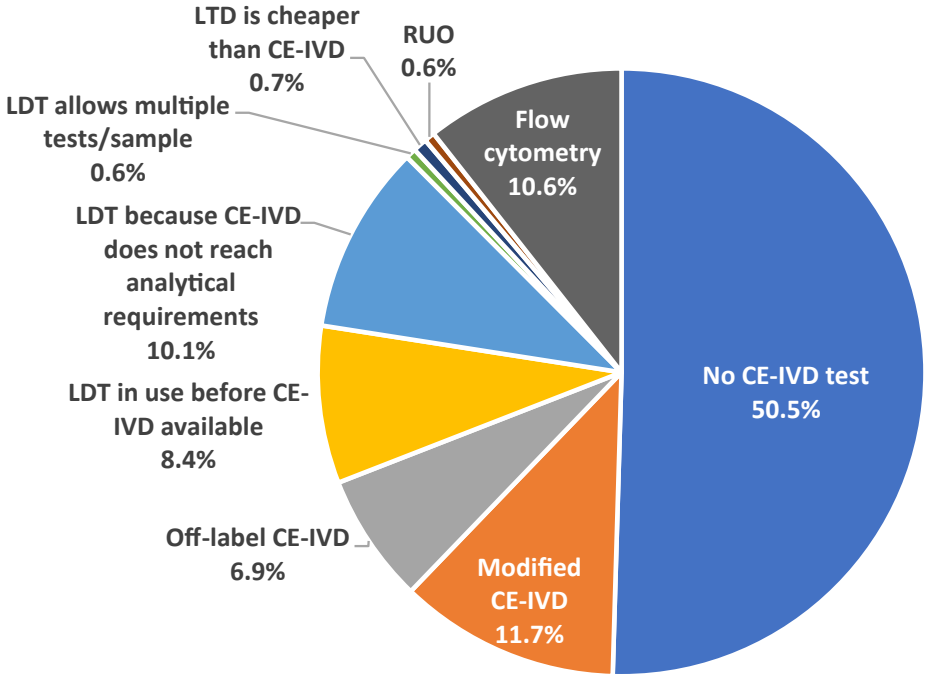
Figure 5: Tests carried out at University Hospitals Leuven



Source: Vermeersch17

The study revealed that the special chemistry area is where most of the LDTs are carried out. In this area, only 11.7% of tests were CE-IVDs. Just over half of the LDTs were done because there were no suitable CE-IVD tests available (Figure 6), while one in ten of the LDTs were flow cytometry tests. According to the researchers at University Hospitals Leuven, "recently, CE-IVD labeled tubes have come on the market which contain a number of frequently used diagnostic antibody panels, but the data analysis is complex and laboratories still have to use lab-developed antibody panels since not all panels are available."

Figure 6: Reasons for not using a CE-IVD test according to the manufacturer's instructions and CE-IVD claim (special chemistry category)



Source: Vermeersch[17]

Using University Hospitals Leuven as an example, of the 922 tests carried out in the laboratories, 537 are modified or off-label IVDs, RUOs or LDTs. These will have to be replaced with CE-marked IVDs, or their use will have to be justified and the justifications documented. The laboratories will also have to monitor and document their use. This will require a lot of time and effort on the part of the laboratory staff.[17]

Stepping up to the challenge of the IVDR is substantial for manufacturers. But for those that are able to ensure that all of their products can be CE-marked, there will be opportunities to extend their markets by providing the support that laboratories need. Companies that can provide a one-stop shop and technical support for clinical chemistry and flow cytometry laboratories, thereby ensuring that the laboratory's workflow can continue without interruption, at an affordable price and without requiring separate equipment for every test, will find new market opportunities.

To meet this need, manufacturers will need to transform all of their non-CE-marked IVD technologies into ones that are fully compliant with the IVDR, but this will offer an opportunity for them to tie reagents, tests and equipment together more closely. Manufacturers can create new CE-marked and compliant products and technologies to fill the gaps. This may include picking up some of the lesser-used IVDs being divested by companies that cannot afford to continue them, or creating new tests to replace LDTs that might otherwise be lost. CE marking reagents and products will also allow laboratories to continue carrying out LDTs that are covered by the IVDR.

CASE STUDY

Barbara Buldini, University of Padua, Italy

Barbara Buldini and her team at the Laboratory of Pediatric Hematology-Oncology in the School of Medicine and Surgery, University of Padua, Italy, use flow cytometry to diagnose and monitor children with acute leukemias.

"We host the centralized laboratory for Italy. Every child in the country with acute leukemia, such as acute myeloid leukemia [AML] or acute lymphocytic leukemia [ALL], has their diagnosis confirmed here through flow cytometry of blood, bone marrow, CSF or tissue samples," says Buldini. "We also use other approaches such as cytogenetics."

Buldini's team use flow cytometry to clarify diagnoses that are ambiguous, and to measure minimal residual disease [MRD] following treatment to better understand prognosis in acute leukemia. Overall, the laboratory carries out around 5000 tests a year.

As well as routine diagnostics work, the department carries out research into the diagnosis and monitoring of acute leukemias. Published work includes analysis of the use of flow cytometric immunophenotyping to assess its impact on clinical management, appraisal of surrogate markers in immunophenotyping to improve diagnosis, and assessment of the prognostic significance of minimal residual disease measured by flow cytometry.

"We work with international groups and share our results among the participants," says Buldini. "These projects include seeking new antibodies for minimal residual disease detection, and searching for better combinations."

Like many diagnostics laboratories, the Padua Laboratory of Pediatric Hematology-Oncology uses both commercial tests and laboratory-developed tests. The advent of the IVDR means that Buldini is beginning the process of auditing the laboratory's roster of tests to assess how they align with the new regulations.

"While we use a lot of antibodies for diagnosis, most of these are certified, so I don't think the impact will be too great. We may not have to make too many changes."

She thinks the greatest challenges will be where individual certified antibodies are used together but the combination is not certified, or where diagnostics companies do not have the test kits available to meet their needs.

"Using cytometry equipment that is certified for diagnostics will help us when we get to the certification step, and will also improve our workflow," she says.

THE ROLE OF THE MANUFACTURER

Manufacturers can also promote awareness and restate the focus on patient safety. But communication of the changes is creating another challenge – it's not clear yet whether all of the resources required for the IVDR are in place from the EU's perspective, or whether all laboratories and small manufacturers are sufficiently aware of the approaching deadlines.

Beckman Coulter has already started reaching out to its customers and pointing them towards information sources. In feedback, it was found that some customers are aware and see the new regulation as a positive move, with tighter controls promising better patient safety, and post-marketing surveillance making both the manufacturer and the laboratory accountable. Others are concerned about the change, or have little awareness of what is coming and how it will impact them.

Beckman Coulter started work on compliance with the new IVDR back in 2016, as part of an intensive worldwide program across all of its business units (Figure 7).[23]

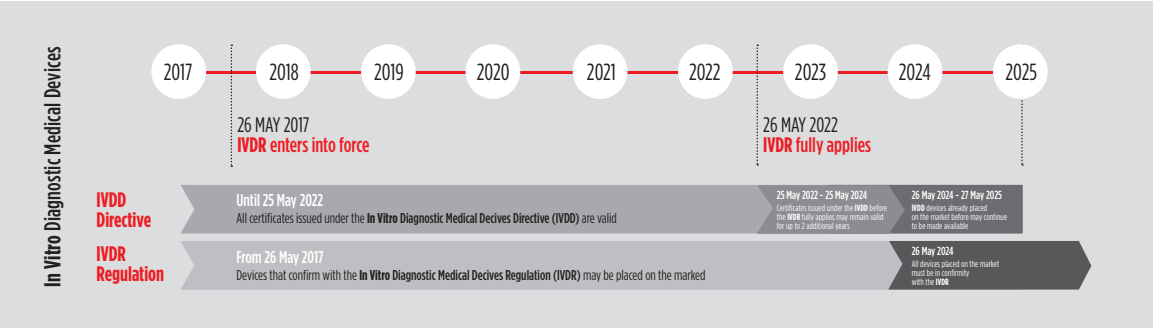


Figure 7: IVDR Transition Timeline

While starting early could be considered a risk, because the regulation wasn't fully clear at the time, the company now believes this was the right choice. Work is still ongoing, but the company plans to fulfil IVDR requirements for the more than 300 CE-marked IVD tests, equipment and reagents in its flow cytometry business unit by May 2022. This has been a significant project, as some current products have been on the market for 30 years, and these have required literature searches and additional studies to ensure that data for all of the clinical performance, scientific validation and clinical evidence requirements are in place. The project has relied on a good relationship between stakeholders across the company, including teams in quality and regulatory affairs, R&D, manufacturing, engineering and marketing.[23]

The impact of the COVID-19 pandemic

The COVID-19 pandemic of 2020 has also caused delays in the preparations for the IVDR, because of local and national lockdowns, increased test workloads for manufacturers and laboratories, staff sickness and self-isolation, and delays to the supply chains. The focus of the EU and member states has obviously shifted towards handling the public health crisis. The EU has already delayed the implementation of the MDR, due to come into force on 26 May 2020, for a year to 26 May 2021, which it attributed to the COVID-19 outbreak and associated public health crisis. The Medical Device Coordination Group has also allowed notified bodies to carry out remote audits.[24-26]

If the IVDR implementation is not delayed, this leaves only a one-year gap between the MDR and IVDR being put into place, rather than the planned two. It could also lead to even more serious bottlenecks with notified bodies than expected. Delaying the enforcement date would also give manufacturers and laboratories more time to get familiar with the IVDR; while some are ahead of the curve, others still aren't fully ready. If tests are not fully certified by the IVDR deadline, this could have a huge and potentially life-threatening impact on patients across Europe.[25]

In July 2020, MedTech Europe, the medical technology industry trade association, raised concerns that parts of the IVDR infrastructure had not yet been put in place, further delayed by the COVID-19 pandemic. These include a lack of notified bodies, guidance documents, EU reference laboratories and common specifications.[6,7] It is urging the EU, the European Commission and member states to put in place measures that will make the IVDR workable. These could include:[25]

- A clear implementation plan, based on discussions with stakeholders
- Extending the grace period for existing tests
- Phasing in the IVDR and strengthening the IVDD
- Postponing the date of application.

Manufacturers will play an important role in supporting their customers through the challenges of the IVDR, and through the additional unknowns of the COVID-19 epidemic.

REFERENCES

1. EU. Regulation (EU) 2017/746 of the European Parliament and of the Council on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU. European Union. (5 April 2017). Available from: https://eur-lex.europa.eu/eli/reg/2017/746/oj.
2. MHRA. An introductory guide to the medical device regulation (MDR) and the in vitro diagnostic medical device regulation (IVDR). Medicines and Healthcare Products Regulatory Agency. (29 August 2017). Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/640404/MDR_IVDR_guidance_Print_13.pdf.
3. EU. Council Directive 93/42/EEC concerning medical devices. European Union. (14 June 1993). Available from: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:EN:PDF.
4. EU. Directive 98/79/EC of the European Parliament and of the Council on in vitro diagnostic medical devices. European Union. (17 October 1998). Available from: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1998L0079:20090807:EN:PDF.
5. BSI. A guide to the In Vitro Diagnostic Directive. British Standards Institution. (2012). Available from: https://www.bsigroup.com/meddev/LocalFiles/en-IN/Technologies/BSI-md-ivd-diagnostic-directive-guide-brochure-UK-EN.pdf.
6. MHRA. Guidance on the In Vitro Diagnostic Medical Devices Directive 98/79/EC. Medicines and Healthcare Products Regulatory Agency. (August 2013). Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/404335/In_vitro_diagnostic_medical_devices_-_guidance_on_legislation.pdf.
7. Cardoso R. New EU rules to ensure safety of medical devices. European Commission. (5 April 2017). Available from: https://ec.europa.eu/commission/presscorner/detail/en/MEMO_17_848.
8. EC. Medical devices - sector: New regulations. European Commission. 2017. Available from: https://ec.europa.eu/health/md_sector/new_regulations_en. Accessed: 16 July 2020.
9. CAMD. FAQ – IVDR Transitional provisions Competent Authorities for Medical Devices Transition Subgroup. (5 January 2018). Available from: http://www.camd-europe.eu/wp-content/uploads/2018/05/FAQ_IVDR_180117_V1.0-1.pdf.
10. EU IVDR. EU IVDR Wiki. 2020. Available from: http://www.euivdr.com/. Accessed: 24 August 2020.
11. Reinikainen M, Suppo M. Explaining IVD classification issues. BSI. (2020). Available from: https://www.bsigroup.com/globalassets/meddev/localfiles/fr-fr/whitepapers/md-classification_issues_for_ivd.pdf.
12. Kennel NJ. *How Europe's New IVD Regulations Will Impact Labs: Ask the Expert*. Clinical Laboratory News, 1 July 2020. Available from: https://www.aacc.org/publications/cln/articles/2020/july/how-europes-new-ivd-regulations-will-impact-labs.

13. Theisen T. *New EU-regulation for in vitro diagnostics*. TÜV SÜD Product Service, 30 January 2018. Available from: https://www.nweurope.eu/media/2818/praesentation_new-eu-regulation-for-in-vitro-diagnostics.pdf.

14. Conway E. *IVD Regulation: What you need to know*. BSI, 5 May 2017. Available from: https://www.bsigroup.com/LocalFiles/es-MX/dispositivos-medicos/BSI-md-IVDR-resumen-webinar-06-05-2017.pdf.

15. FDA. Unique Device Identifier System: Frequently Asked Questions, Vol. 1. Food and Drug Administration. (August 2014). Available from: Unique Device Identifier System: Frequently Asked Questions, Vol. 1.

16. EC. Nando notified bodies database. European Commission. 2020. Available from: https://ec.europa.eu/growth/tools-databases/nando/index.cfm?fuseaction=directive.notifiedbody&dir_id=35. Accessed: 17 September 2020.

17. Vermeersch P, Van Aelst T, Dequeker EMC, The new IVD Regulation 2017/746: a case study at a large university hospital laboratory in Belgium demonstrates the need for clarification on the degrees of freedom laboratories have to use lab-developed tests to improve patient care. *Clin Chem Lab* Med 2020. 10.1515/cclm-2020-0804.

18. SGS. Medical & in vitro diagnostic CE marking process. SGS. (February 2019). Available from: https://www.sgs.com/-/media/global/documents/technical-documents/technical-bulletins/sgs-cbe-price-and-fees-for-sgs-public-website-1905v4.pdf?la=en.

19. Genzen JR, Regulation of Laboratory-Developed Tests. *Am J Clin Pathol* 2019. 152(2): p. 122-131. 10.1093/ajcp/aqz096.

20. FDA. Laboratory Developed Tests. Food and Drug Administration. (27 September 2018). Available from: https://www.fda.gov/medical-devices/vitro-diagnostics/laboratory-developed-tests.

21. Ezzouaouy B. IVD-R Annex I Global Safety and Performances Requirements (GSPR). A New Set of Requirements for Clinical Laboratories Performing Laboratory Developed Tests. Beckman Coulter. (2020).

22. Pereira P. *ISO 15189:2012 Medical laboratories - Requirements for quality and competence*. Westguard QC, February 2017. Available from: https://www.westgard.com/iso-15189-2012-requirements-1.htm.

23. Nieto L, Vernier J, Jusdado F, *et al.* IVDR: a new era for In-Vitro Diagnostic Medical Devices. Beckman Coulter. (2020). Available from: https://www.beckman.com/gated-media?mediaId={BEC54E85-ABAB-485F-8BEC-297C142ADCB9}.

24. Parrone J. Press release: MedTech Europe urges EU authorities to make IVD Regulation implementation workable. MedTech Europe. (9 July 2020). Available from: https://www.medtecheurope.org/news-and-events/press/medtech-europe-urges-eu-authorities-to-make-ivd-regulation-implementation-workable/.

25. Staff writer. Ensuring a successful transition to the new IVD Regulation in light of COVID-19. MedTech Europe. (9 July 2020). Available from: https://www.medtecheurope.org/resource-library/ensuring-a-successful-transition-to-the-new-ivd-regulation-in-light-of-covid-19/.

26. Rachal M. *It's official: EU finalizes 1-year MDR delay*. MedtechDive, 24 April 2020. Available from: https://www.medtechdive.com/news/its-official-eu-finalizes-1-year-mdr-delay/576724.

Appendix

Abbreviations	
CA	Competent authority
CE	Conformité Européenne
CS	Common specifications
DoC	Declaration of conformity
EEA	European Economic Area
EFTA	European Free Trade Association
EU	European Union
Eudamed	European database on medical devices
FSCA	Field safety correction action
GSPR	General safety and performance requirements
IFU	Indication for use
IVD	In vitro diagnostic
IVDD	In Vitro Diagnostic Medical Devices Directive 98/79/EC
IVDR	In Vitro Diagnostic Regulation (EU) 2017/746
LDT	Laboratory developed test
MDR	Medical Device Regulation
MDCG	Medical Device Coordination Group
NB	Notified body
NBOG	Notified Body Operations Group
PER	Performance evaluation report
PMPF	Post market performance follow up
PMS	Post market surveillance
PRRC	Person responsible for regulatory compliance
PSUR	Periodic safety report
SSP	Summary of safety and performance
UDI	Unique device identifier
Nando	New Approach Notified and Designated Organizations

Definitions	
Authorized representative	Someone within the EU who has a written mandate from a manufacturer outside the EU to act on the manufacturer's behalf under the IVDR
CE	Compliance to all European regulations applicable to a product sold on European countries
CE marking	Marking that indicates that a device conforms with the IVDR and other appropriate EU legislation
Companion diagnostic	Device which is essential for the safe and effective use of a corresponding medicinal product
Competent Authority	A body within the government, often the ministry of health, that ensures that EU regulations are transposed into national legislation
Conformity assessment	The process demonstrating that the IVDR requirements have been fulfilled
Conformity assessment body	The third party that carries out conformity assessments
Distributor	Someone within the EU, other than the manufacturer or importer, who makes a device available on the market
Economic operator	A manufacturer, an authorized representative, an importer, or a distributor
GSPR	List of all the requirements that an IVD product sold on the European country shall satisfy
Health institution	An organization that cares for or treats patients, or promotes public health
Importer	Someone within the EU who places a device from a third country on the market in the EU
In vitro diagnostic device	Reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system to be used in vitro for the examination of specimens, including blood and tissue donations, to provide information on: physiological or pathological processes or states; congenital physical or mental impairments; predisposition to a medical condition or a disease; safety and compatibility with potential recipients; treatment response or reactions; therapeutic measures
LDT	An in vitro diagnostic testing procedure designed, manufactured, and used within a single laboratory, typically using a commercially available in vitro diagnostic
Medical device	Instrument, apparatus, appliance, software, implant, reagent, material or other for diagnosis, prevention, monitoring, prediction, prognosis, treatment, alleviation or compensation for disease, injury or disability, which does not use pharmacological, immunological or metabolic means for its principal intended action
Notified body	Independent conformity assessment bodies designated by a national Competent Authority. Perform third-party conformity assessment activities including calibration, testing, certification, and inspection
Post-market surveillance	Collection and review of data on devices on the market to identify needs for corrective or preventive actions, and to confirm that benefits still outweigh risks
Unique device identifier	A code of numbers or letters and numbers created through internationally accepted device identification and coding standards that allows identification of specific devices on the market
Vigilance	Identification, reporting and trending of serious incidents and conduct of safety related corrective actions
Person responsible for regulatory compliance	An individual or individuals who check the conformity of devices before release, prepare and maintain documentation, and ensure that post-market surveillance and vigilance reporting is carried out

Annex II of the IVDD

List A

- Reagents and reagent products, including related calibrators and control materials, for determining the following blood groups: ABO system, rhesus (C, c, D, E, e) anti-Kell
- Reagents and reagent products, including related calibrators and control materials, for the detection, confirmation, and quantification in human specimens of markers of HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C and D.

List B

- Reagents and reagent products, including related calibrators and control materials, for determining the following blood groups: anti-Duffy and anti-Kidd
- Reagents and reagent products, including related calibrators and control materials, for determining irregular anti-erythrocytic antibodies
- Reagents and reagent products, including related calibrators and control materials, for the detection and quantification in human samples of the following congenital infections: rubella, toxoplasmosis
- Reagents and reagent products, including related calibrators and control materials, for diagnosing the following hereditary disease: phenylketonuria
- Reagents and reagent products, including related calibrators and control materials, for determining the following human infections: cytomegalovirus, chlamydia
- Reagents and reagent products, including related calibrators and control materials, for determining the following HLA tissue groups: DR, A, B
- Reagents and reagent products, including related calibrators and control materials, for determining the following tumoral marker: PSA
- Reagents and reagent products, including related calibrators, control materials and software, designed specifically for evaluating the risk of trisomy ^{21}
- The following device for self-diagnosis, including its related calibrators and control materials: device for the measurement of blood sugar

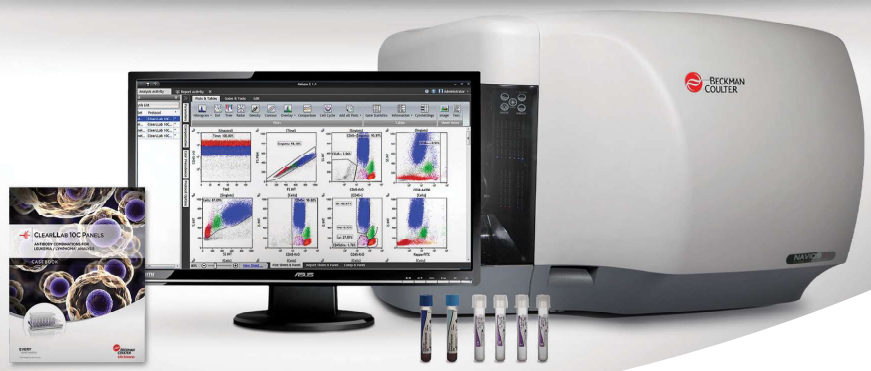
Annex VI, Part B of the IVDR

CORE DATA ELEMENTS TO BE PROVIDED TO THE UDI DATABASE TOGETHER WITH THE UDI-DI IN ACCORDANCE WITH ARTICLES 25 AND 26

The manufacturer shall provide to the UDI database the UDI-DI and the following information relating to the manufacturer and the device:

1. quantity per package configuration,
2. the Basic UDI-DI as referred to in Article 24(6) and any additional UDI-DIs,
3. the manner in which production of the device is controlled (expiry date or manufacturing date, lot number, serial number),
4. if applicable, the 'unit of use' UDI-DI (where a UDI is not labelled on the device at the level of its 'unit of use', a 'unit of use' UDI-DI shall be assigned so as to associate the use of a device with a patient),
5. name and address of the manufacturer, as indicated on the label,
6. the SRN issued in accordance with Article 28(2),
7. if applicable, name and address of the authorized representative (as indicated on the label),
8. the medical device nomenclature code as provided for in Article 23,
9. risk class of the device,
10. if applicable, name or trade name,
11. if applicable, device model, reference, or catalogue number,
12. additional product description (optional),
13. if applicable, storage and/or handling conditions (as indicated on the label or in the instructions for use),
14. if applicable, additional trade names of the device,
15. labelled as a single use device (y/n),
16. if applicable, the maximum number of reuses,
17. device labelled sterile (y/n),
18. need for sterilization before use (y/n),
19. URL for additional information, such as electronic instructions for use (optional),
20. if applicable, critical warnings or contra-indications,
21. status of the device (on the market, no longer placed on the market, recalled, field safety action initiated).

ALL THE PIECES ARE IN PLACE.



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