cytognos
Flow Cytometry Solutions

YOUR GUIDE TO THE NEW EUROPEAN IVD REGULATION

In May 2017, the European Union published the In Vitro Diagnostic Medical Devices Regulation EU 2017/746 **(IVDR)** which repeals the In Vitro Diagnostic Medical Devices Directive 98/79/EC **(IVDD)** in order to establish a more robust, transparent, predictable and suitable regulatory framework for IVD Medical Devices.

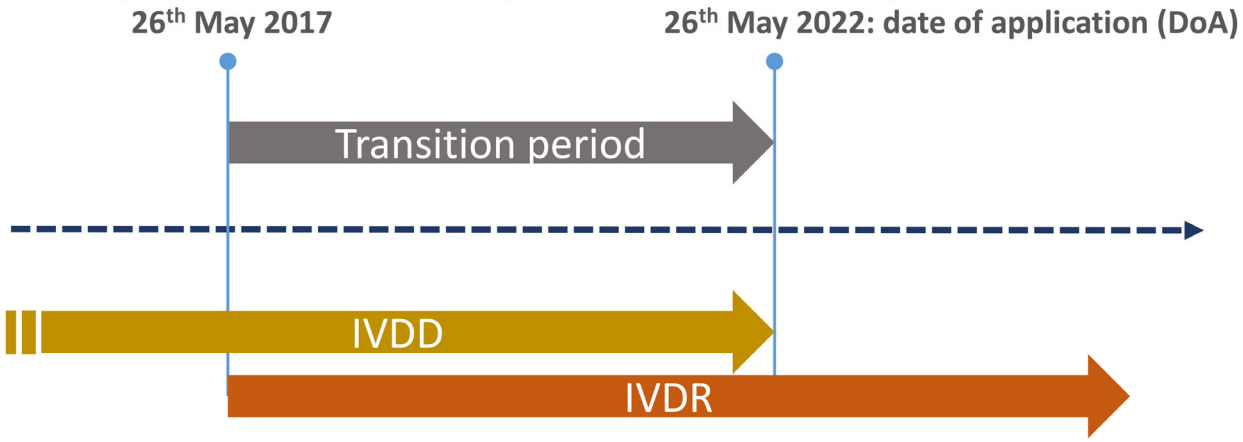
The **aim** of **IVDR** is to guarantee patient safety by enforcing **transparency, traceability** and heightening the requirements to demonstrate **clinical evidence** and **analytical performance** of CE-IVD Medical Devices, which ensures a high level of safety and health whilst supporting innovation.

CURRENT LANDSCAPE

	It affects...
IVDD (IVD Directive)	Manufacturers
IVDR (IVD Regulation)	Economic Operators* and Health Institutions (e.g. Clinical Laboratories performorming LDTs)

*Economic Operators: manufacturers, distributors and importers

IVDR TRANSITION TIMELINE



EMBRACE NEXT GENERATION FLOW

A COMPLETE SOLUTION FROM SAMPLE PREPARATION TO EXPERT-GUIDED AUTOMATED REPORTING

This document does not purport to be an interpretation of regulation and is for guidance purposes only

HOW IVDR WILL AFFECT CLINICAL FLOW CYTOMETRY LABORATORIES?

- It will be mandatory to use CE-IVD products developed under IVD Regulation (IVDR) commercially available.
- The use of laboratory developed test (LDTs) will only be allowed in two scenarios:
  - When non-equivalent* CE-IVD test developed under IVD Regulation is commercially available.
  - When the commercially available CE-IVD test does not fit specific clinical needs.

The laboratory should carefully, extensively and rigorously justify the use of the LDT to the competent authority.

*According to the IVD Regulation, a device is considered as equivalent when, based on a review of publicly available product data, the device in question is either almost identical to the comparator device or identical to the comparator device regarding the product composition, design, features, and intended purpose.

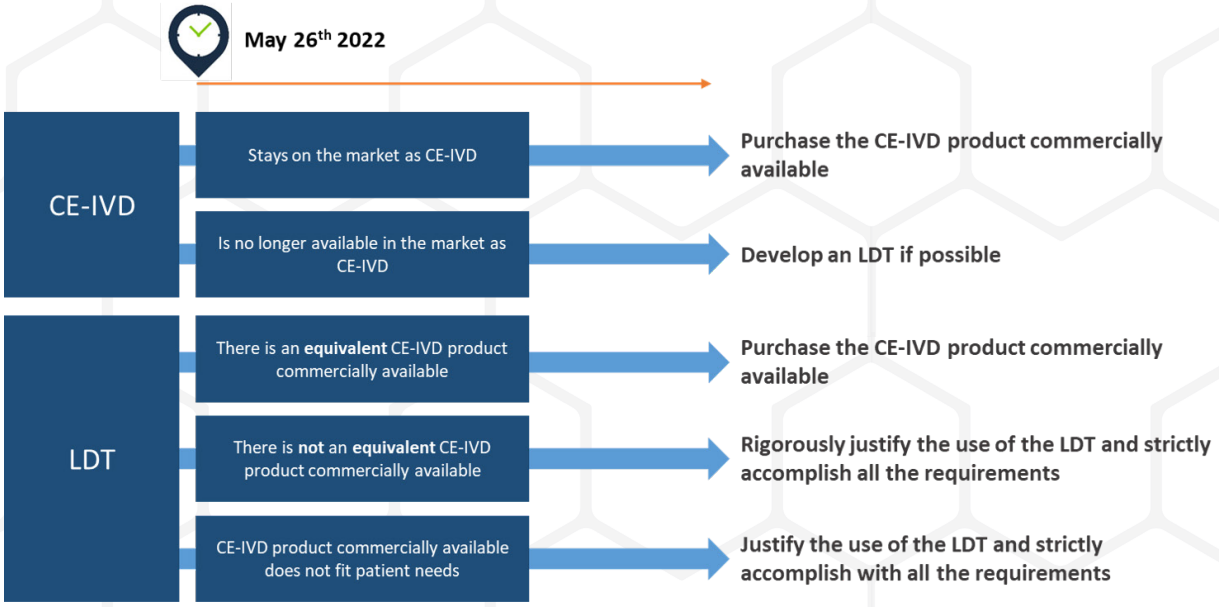


Figure 1. Impact of IVDR on CE-IVD products and LDT

WHAT IS CONSIDERED AN LDT?

- An in-house test developed and manufactured by the laboratory, including any test using single antibodies to build panels even though those are recommended and validated by scientific consortia.

- The use of a CE-IVD labelled test commercially available for a different intended use (off-label use). This includes the use of the test in a different application than the one stated by the manufacturer, e.g. the use of a test designed for disease diagnosis applied to the assessment of minimal residual disease. Also, the use of the test on a different type of biological sample from the indicated by the manufacturer. For example, the use of the test on peripheral blood when it is indicated for use on bone marrow.

- The use of a CE-IVD labelled test commercially available modified in the laboratory. The following are some examples of what can be considered a modification by the laboratory:
  - Add additional antibodies to complete the CE-IVD test.
  - Include any relevant modification to the protocol including modifications to equipment calibration, compensation or sample preparation. In this sense, a change in incubation times, buffers or sample staining could be considered a modification of the test.
  - Reagent dilutions. This includes the use of less reagent than the amount recommended by the manufacturer.

HOW CAN FLOW CYTOMETRY LABORATORIES USE AND DEVELOP LDTS FROM MAY 26th, 2022?

The following steps are mandatory for clinical laboratories when developing an LDT:

- Justify the use of the LDT: prove that there is not an equivalent CE-IVD test developed under IVD Regulation commercially available.
- Strictly accomplish all requirements related to the **product** and to the **health institution:**

PRODUCT REQUIREMENTS

- **Classify the test** according to Annex VIII of the IVDR:

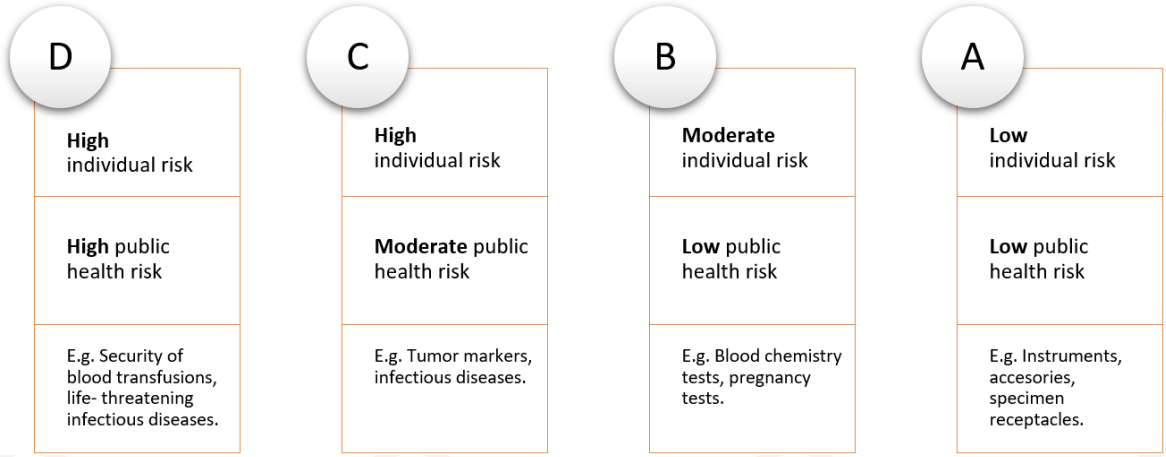


Figure 2. Classification of test according to Annex VIII of the IVDR

  - Antibody panels used for screening, diagnosis or staging of cancer are considered Class C (Annex VIII).
  - Instruments, such as flow cytometers, are considered Class A.

- **Demonstrate compliance with Annex I requirements** with scientific evidence, analytical and clinical performance tests and/or published literature. The laboratory must demonstrate that the product meets the general requirements for safety and performance. The demonstration of compliance with the requirements of Annex I shall be made based on a risk analysis. A higher risk implies more thorough tests to demonstrate compliance with the requirements. Although the regulatory requirements are the same for all classes, analytical and/or clinical tests will be dependent on their nature and risk . For example, it will not require the same analytical tests to demonstrate the performance of a lysis solution (class A) than a cancer related diagnostic test (class C). The latter will require the evaluation of pathological samples and a larger number of samples. Similarly, the lysis solution will normally have no cut-off values, no limit of detection, no limit of quantification, and no clinical performance.
- The Annex I includes **71 different sections**: 20 general items and 51 subsections.

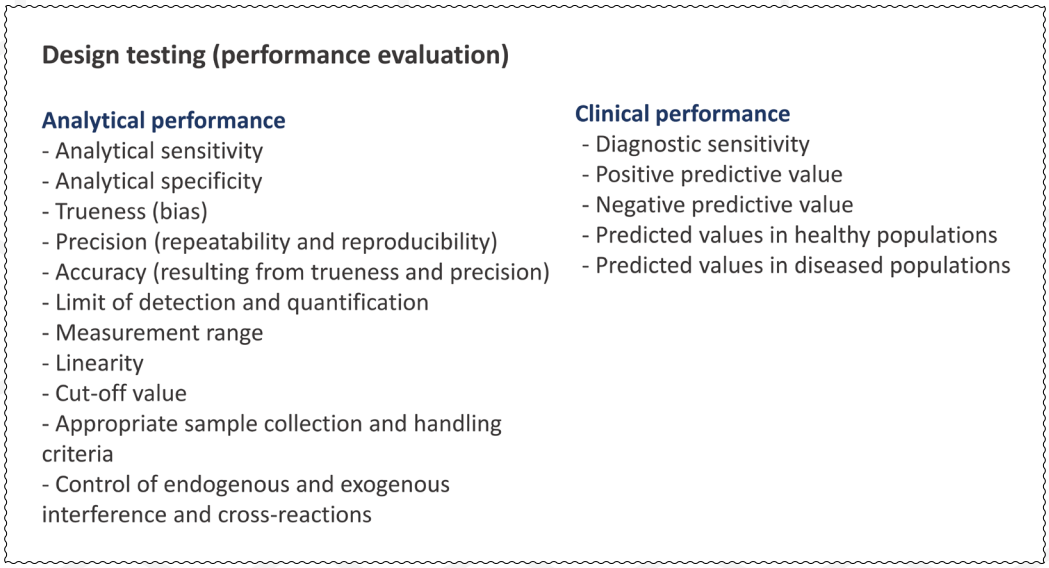


Figure 3. Performance evaluation tests required in Section 9.1 of Annex I

- LDTs must be **manufactured and used in the health institution**, they cannot be transferred nor can they be manufactured on an industrial scale.
- **Document** that the specific clinical needs cannot be met with another CE-IVD product commercially available.
- **If requested, inform the competent authority** of the use of the product along with justification for its manufacture and use.
- For Class D tests: prepare documentation of **manufacture, design and performance data** to the competent authority that will check if the requirements of Annex I are met.

HEALTH INSTITUTION REQUIREMENTS

- Manufacture and use of the test under **Quality Management Systems**.
- Must comply with **ISO 15189** (Quality System in clinical laboratories).
- **Public declaration** that the products comply with the requirements of Annex I.
- **Continuous evaluation of the LDT performance** with the clinical use and implement corrective actions if needed.

Member States may require laboratories to submit to the competent authority any additional relevant information on the products that have been used. They can restrict the manufacture and use of any LDT and shall be allowed access to the activities of health facilities for inspection purposes.

IMPORTANT CLARIFICATIONS FOR LABORATORIES

- Each institution has to perform its **own validations**. The documentation provided by another center cannot be used for this purpose. An LDT that has not been manufactured by your own healthcare institution cannot be used.
- If an LDT is developed and validated, there is a **risk that a commercially available CE-IVD test eventually appears**. In this case, there are two options: 1) it will be mandatory to stop using the LDT and start using the CE-IVD commercial test or 2) the need for using the LDT against the commercial CE-IVD test will have to be rigorously justified again.
- Having ISO 15189 accreditation in force is a requirement to be able to develop an LDT, but **in no case is it a sufficient condition for the use of an LDT**.

LABORATORY RESOURCES USED FOR ACCREDITATION OF EACH LDT

TIME

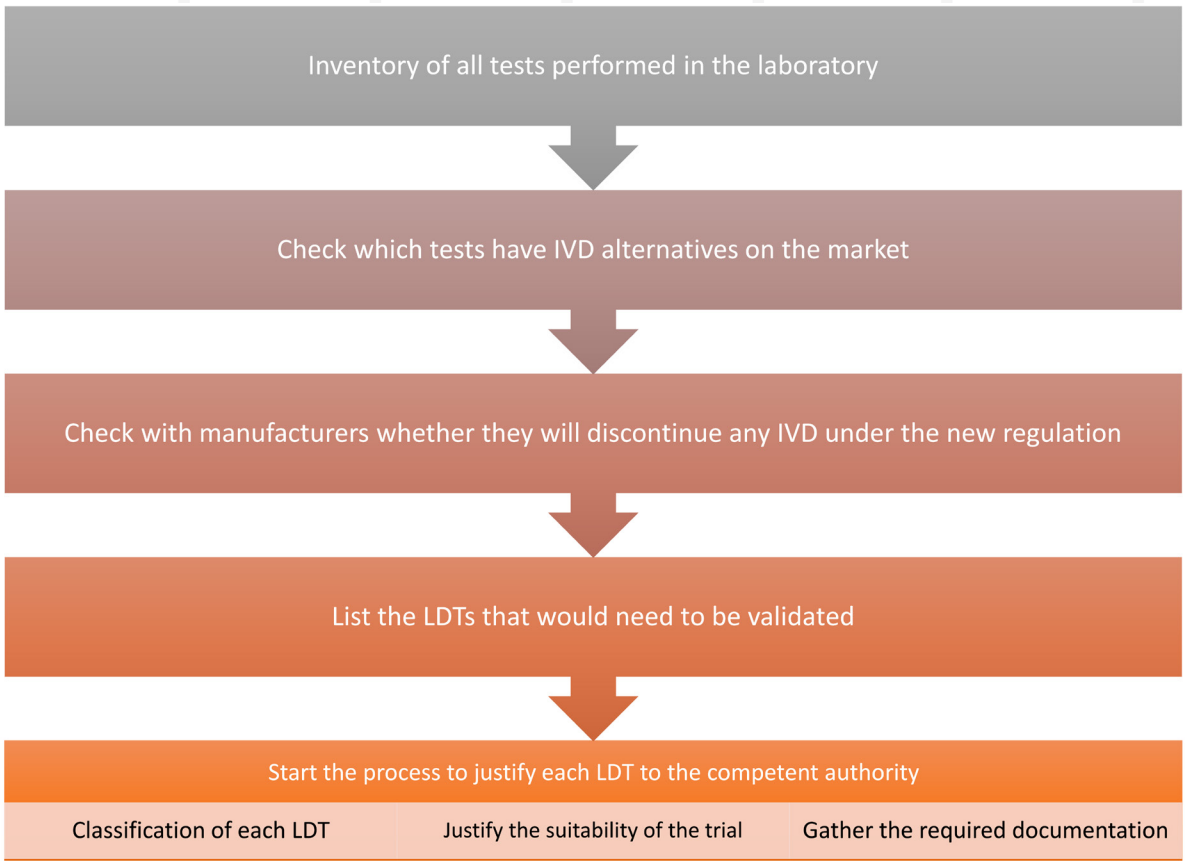
To get an approximate idea of the time it takes to develop an LDT, the following steps should be taken into account:

- Unravel requirements and define tests to be done.
- Analytical testing. This includes gathering all materials, reagents and equipment necessary to carry out the relevant tests, including stability.
- Clinical evaluations. Depending on access to patient or donor samples, the process may take longer.
- Prepare documentation. Once all relevant tests have been completed, all required documentation must be completed and submitted.

GENERAL COST

- Cost of all analytical and clinical tests (reagents and equipment).
- Cost of elaborating and presenting all the information to the competent authority if required (according to the specifications by the Member States).
- General cost associated to personnel.

ACTION PLAN FOR CLINICAL FLOW CYTOMETRY LABORATORIES



YOU ARE NOT ALONE TO FACE THIS CHANGE

Cytognos offers extensively validated panels and in order to continue to guarantee the quality and availability of our products, we are working hard to continue offering our diagnostic kits and antibodies, Infinicyt™ and Omnicyt™ under the IVDR regulation from May 26th 2022.

Moreover, the gained experience in the process of validating our own products under this regulation, can serve as an orientation (industrial standard) for the clinical laboratories that have to validate their own LDTs.

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