Guide to the In Vitro Diagnostic Medical Devices Regulation (EU) 2017/746

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Background

The In Vitro Diagnostic Directive (IVDD 98/79/EC) was introduced two decades ago to define the requirements for marketing IVD products in the European Union. Under the directive, the majority of IVD products were self-certified and not subject to oversight by a Notified Body, and some IVDs were not even addressed in this directive. Innovation in life-sciences developed rapidly and it became clear to European regulators that the IVDD was largely inadequate in the fast-changing world of medical diagnostics technology.

Over the years, several flaws in the system of Notified Bodies (NBs) were exposed and it became clear that the system needed an overhaul. In addition, the IVDD lacked alignment with international guidelines regarding IVDs.

As a result, the In Vitro Diagnostic Regulation (2017/746) or "IVDR" was developed to employ a stricter oversight that will encompass many more products. The requirements are now a regulation, rather than a directive, which means that it is legally binding in EU countries. IVDR is longer and expands the scope of compliance to cover more products as well as define requirements for Notified Bodies. The IVDR follows a life-cycle approach, demonstrated by incorporating the MEDDEV guidances and introduces many new concepts and requirements.

The IVDR is about 4 times longer than the IVDD it replaces. It contains 10 chapters that are comprised of articles (113 in total) and 15 annexes.

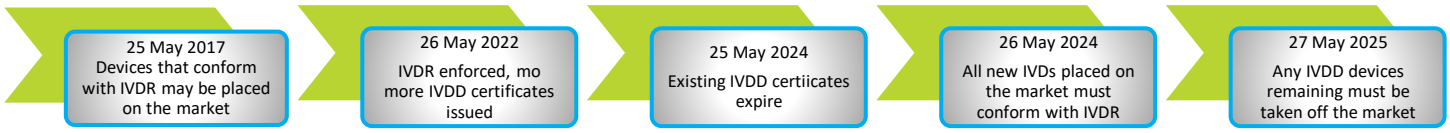
In Vitro Diagnostic (IVD) Definition*

'In vitro diagnostic medical device' means any medical device which uses reagents and their products, calibrators, control materials, kits, instruments, apparatus, equipment, software and/or system to examine bodily specimens, such as blood, saliva, urine or tissue, derived from the human body.

*A full definition can be found in Article 2(2) of the IVDR

The IVDR Transition Period

The IVDR officially came into force in 25 May 2017 with a five-year transition period to full implementation, meaning that it only fully applies from 26 May 2022. The timeline for this transition is outlined in Article 110 of the IVDR. During the transition period, IVDs may be put on the market under the IVDD or the IVDR. By 27 May 2024, all CE certificates under the IVDD will become void, if not before.



What are the major IVDR changes?

There are many changes in the IVDR and it is the responsibility of the manufacturer to ensure its products are in compliance. We will outline the major changes here and go into more detail later:

- IVDR uses a risk-based approach to classification: Classes A, B, C, and D. (Chapter V & Annex VIII of the IVDR describe the classification system). This classification is based on the Global Harmonization Task Force (GHTF) classification system bringing the EU regulations into alignment with global classification of IVDs. As a result of this new classification system, the majority of IVDs will now require the involvement of a Notified Body in Europe.
- The requirement for a quality management system and technical documentation to be reviewed by a Notified Body will apply to IVD classes B, C and D. Manufacturers of these devices will be subject to unannounced audits by the NB. (Annexes II, III, IX, X, & XI).
- More stringent requirements for the designation of Notified Bodies are introduced, including increased control and monitoring by the competent authorities and the European Commission.
- The IVDR also covers software that is incorporated into IVD instruments, such as

The IVDR also outlines new requirements for NBs including stricter supervision by competent authorities in Europe and currently few NBs have been designated to the IVDR. This, as well as the increased requirement for NB assessment of IVDs will lead to a greater demand for NB services. Plan accordingly!

A list of Notified Bodies can be found on the NANDO website.

Software as a Medical Device (SaMD) and apps.

- There is an increased requirement for clinical and performance studies (Chapter VI & Annexes XIII & XIV).
- The requirements for vigilance and post-market surveillance are stricter (Chapter VII & Annex III).
- Product traceability throughout the supply-chain and labelling identification have received a greater focus with the introduction of the UDI system. (Articles 24-27).
- The requirements for Economic Operators (EO) including Authorized Representatives (AR), importers, distributors and the Person Responsible for Regulatory Compliance (PRRC) are detailed. (Articles 10-16).
- The European Commission will set up a new EUDAMED database to enable transparency by maintaining records of device traceability, clinical investigations, vigilance and surveillance. Its functions and information required to be submitted are outlined in the IVDR. (Article 30). This database is scheduled to go online in May 2022.

Navigating these changes can be challenging, Li-Med's regulatory professionals can help steer you in the right direction.

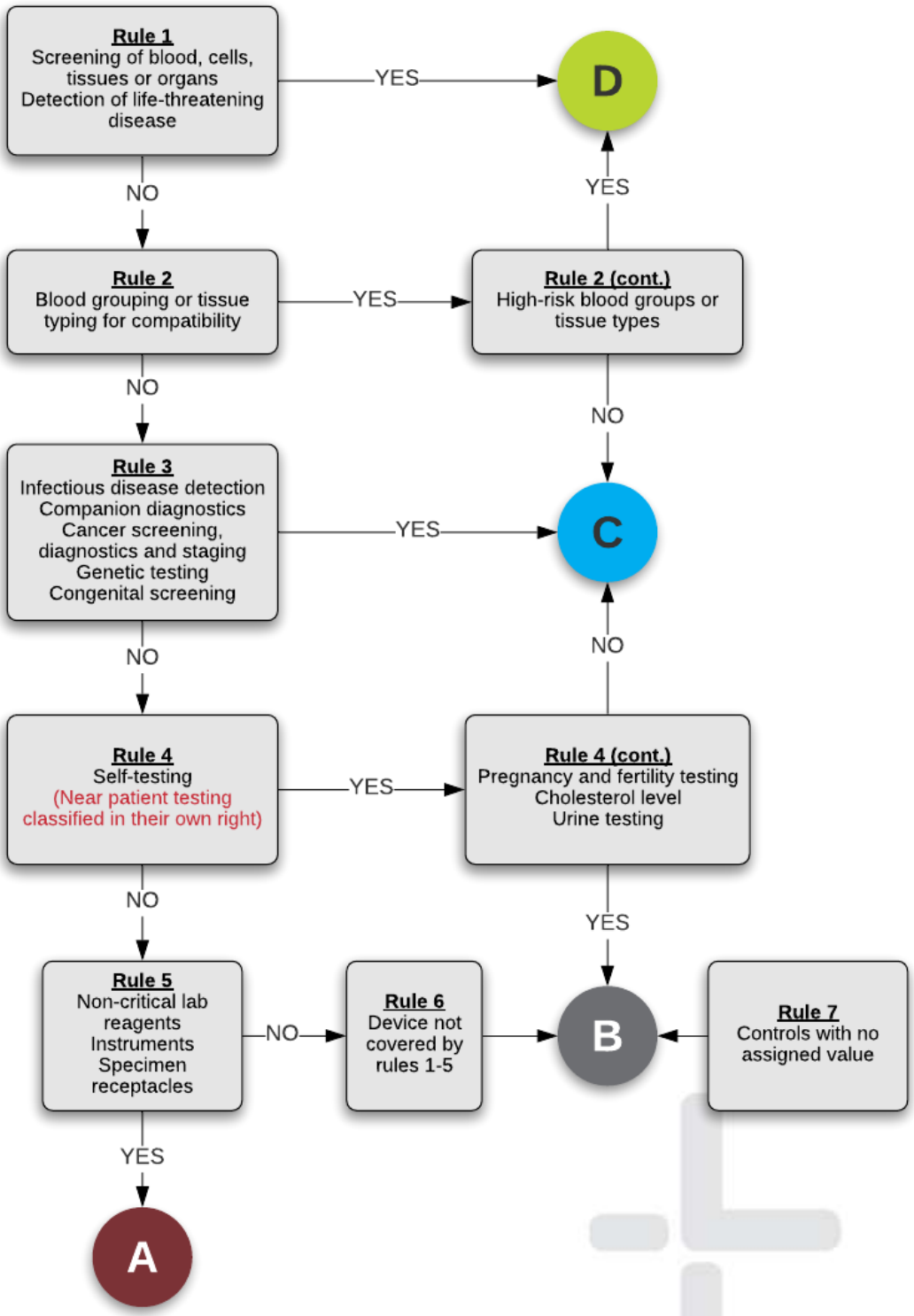
How are IVDs classified?

The IVDR introduces a new classification scheme for IVDs based on GHTF IVD Classification Guidance that is more resilient to changes in technology and medicine. Instead of the IVDD's list-based classification, the IVDR's rule-based classification system divides IVDs into four classes based on their risk profiles. The device classes increase with risk, Class A being the lowest risk and Class D being the highest risk. Classification is determined by the intended purpose and considers the risks to both the individual and public health. Article 47 of the IVDR discusses the classification, and the rules themselves are laid out in Annex VIII. All seven rules must be consulted to determine the device classification the applicable rule leading to the highest classification will apply to the device. Class A non-sterile devices will be self-certified by manufacturers, excluding sterile devices. Class B, C and D devices require conformity assessment by a Notified Body.

> It is highly likely that even if your product was self-certified under the IVDD, it will be up-classified under the IVDR an require NB involvement.

Manufacturers will need to re-assess their product to determine which rules apply and justify the classification. The following flow chart illustrates the application of the classification rules. For an accurate classification of the IVD, please refer to the IVDR Annex VIII.

IVD Classification Flow Chart (IVDR)



What route to Conformity Assessment applies to my IVD?

The IVDR lays out several routes for conformity assessment depending on the risk class of the IVD which are descried in Annexes IX, X and XI. The routes to conformity assessment are based on:

- Quality management system and technical documentation (Annex IX)
- EU Type-examination (includes technical documentation) (Annex X)
- Production quality assurance (Annex XI)

The manufacturer may have some choice in the route to conformity assessment. The following table outlines the available routes depending on the device class. (The exact requirements are detailed in the IVDR):

NBs performing conformity assessment will request an EU reference lab to verify the performance claimed by the manufacturer.

IVD Class (per Annex VIII)	Conformity assessment options		NB involvement	Notes	
Class A	Prepare Technical Documentation (Annexes II and III) EU Declaration of conformity		None (self-declared)	Class A sterile IVDs – NB assess QMS or Production QA of sterile aspects	
Class B	QMS (Annex IX excl. chapter II) **and** Technical Documentation (Annex IX 4.4-4.8)		NB Audit and assessment – sampling of technical documentation per category device		Near-patient testing and self-testing IVDs require technical documentation assessment by NB
	Option 1	**Option 2**			
Class C	QMS (Annex IX excl. chapter II) **and** Technical Documentation (Annex IX 4.4-4.8a	EU Type Examination (Annex X) **and** Production Quality Assurance (Annex XI)	NB Audit and assessment – For **Option 1:** Review of technical documentation of per generic device group	Companion diagnostics require Competent Authority consultation	
Class D	QMS **and** Technical Documentation (Annex IX)	EU Type Examination (Annex X) **and** Production Quality Assurance (Annex XI)	NB Audit and assessment	Performance verification by reference laboratory	

Determining the classification of your IVDs and deciding which conformity assessment route to take is a key factor in compliance with the IVDR. Li-Med can assist in this process to ensure a smooth transition.

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What Technical Documentation will I need to present to the Notified Body?

Annex II details the technical documentation a manufacturer will need to prepare for a Class B, C or D product that will be reviewed by a Notified Body. Even though Class A products will not have their technical documentation reviewed by a NB before they are placed on the market, the manufacturer must still compile this information. Technical documentation must include:

- Device specification, including intended purpose, method of operation, etc.
- Labels and instructions for use
- Design and manufacturing information
- General safety and performance requirements (GSPR) (Annex I)
- Benefit-risk analysis and Risk Management
- Product verification and validation
- Performance Evaluation Report (PER) which includes clinical evidence

The GSPR in Annex I is similar to the Essential Requirements in the IVDD but includes many more requirements and greater detail. Among others, the GSPR includes requirements for performance characteristics, risk management, and specific devices such as electronic programmable systems, self-testing and near-patient testing.

> The GSPR are a core component of the IVDR and provide the criteria for safety and performance applicable to all aspects of IVDs, throughout their life-cycle.

Preparing the technical documentation can place demands on manufacturers; Li-Med's experts can help in easing the burden.

What Clinical and Performance studies do I need to perform?

Chapter VI discusses the requirements for clinical evidence, performance evaluation and performance studies, the details of which are described in Annexes XIII-XIV. The requirement for clinical evidence and post-market performance follow-up are new for IVDs. As mentioned previously, a Performance Evaluation Report (PER) must be included in the technical documentation.

> The Notified Body will review the information in the PER and may request additional testing

The Performance Evaluation must demonstrate the following elements regarding the IVD:

- Scientific validity
- Analytical performance
- Clinical performance

Much of this information can be obtained from scientific literature, but manufacturers must determine if it is adequate and perform necessary tests to fill in the gaps.

The performance evaluation is an on-going process with the purpose of evaluating the IVD throughout

its life-cycle, and will constantly need updating by assessing and analyzing post-market performance follow-up data. The PER of Class C and D IVDs must be updated annually. The PER of Class A and B devices can be updated as needed but it is a good idea to annually review the data to determine if it needs updating.

Information from performance studies is required to be uploaded to the EUDAMED database. The PER is in line with the FDA requirements so if you have an IVD marketed in the US, this documentation should be easy to compile.

Arranging the clinical and performance studies and preparing the performance evaluation report can be daunting; Li-Med's experts can help in determining and arranging the testing.

What are the new requirements for vigilance and Post-Market Surveillance?

The requirements for post-market surveillance, vigilance and market surveillance are outlined in Chapter VII. Manufacturers must gather and analyze data about post-market activities as part of the life-cycle approach to continuously review the benefit-risk analysis of their products. Annex III describes the technical documentation for Post-Market Surveillance required for each product. It includes:

- Post-Market Surveillance Plan which describes the system for gathering, recording and analyzing relevant quality, safety and performance data regarding the IVD throughout its life-time.
- Post-Market Surveillance Report which summarizes the results and conclusions of the analysis of the Post-Market Surveillance data and include any Corrective and Preventative Actions (applies to Class A and B and may be updated as needed)
- Periodic Safety Update Report which includes the same information as the Post-Market Surveillance Report as well as benefit-risk analysis, sales volumes, user population characteristics, and use frequency. (Applies to Class C and D and must be updated annually)

Requirements regarding vigilance and incident reporting are much stricter in the IVDR than the IVDD. The timeframes for reporting serious incidents are laid out in Article 82 and there are new requirements regarding vigilance reporting if there is a significant increase in frequency or severity of incidents. Requirements regarding reporting of and Field Safety Corrective Actions (FSCA) as well as analysis of vigilance information are described in detail. There is a new requirement to submit vigilance reports to the EUDAMED database.

What is the UDI system?

The Unique Device Identifier (UDI) system is introduced in Chapter III to enable consistent and universal identification of medical devices throughout their distribution and use. It is similar to the FDA's UDI system and its purpose is to facilitate device traceability. The idea is to increase the effectiveness of Post-Market Surveillance and improve monitoring by competent authorities. The use of UDIs for traceability should also help protect against falsification of devices. Each device will be designated with a device identifier (UDI-DI), and each batch or production lot will receive a production identifier (UDI-PI). The Basic UDI-DI of a device must be listed on the IVD Declaration of Conformity as well as the CE certificates. There are a number of designated entities which assign the UDIs, and the UDIs must be entered into the EUDAMED database.

What are Economic Operators and the PRRC?

Economic Operators (EO) include manufacturers, authorized representatives (AR), importers and distributors whose obligations are described in the IVDR. The Person Responsible for Regulatory Compliance (PRRC) has the role of ensuring the regulatory compliance of the manufacturer or AR. The PRRC must have appropriate experience and education and bears a huge responsibility. Small companies can outsource the role of the PRRC. In the case of a non-EU based manufacturer, an AR must be contracted and will assume legal liability for defective devices alongside the manufacturer. This means that the AR must be involved in market surveillance, cooperate with the competent authorities in the case of investigations, and ensure that the manufacturer has appropriate conformity assessment (with the use of its own PRRC). EOs must register with the EUDAMED database and obtain an SRN. Chapter II defines the roles and responsibilities of each EO and the PRRC.

> It is the manufacturer's responsibility to ensure the EOs meet their obligations.

Li-Med's regulatory and quality assurance expertise and experience allow us to offer our services as an outsourced PRRC

How should I prepare for the new IVDR?

It may seem as if May 2022, when the IVDR enters into force, is a long way off, but the transition will take time and you should start planning for it now. Here is how:

1. **Determine the class of your IVD products**
   First of all, use the rules in Annex VIII to re-classify your device according to the IVDR. Once you know the device class, you will be able to determine what routes of conformity assessment are available to you and what you need to do to achieve this.
2. **Conduct an IVDR Gap Assessment**
   Once you have determined your IVD class, a Gap assessment will help you find what you need to do to achieve compliance with the IVDR. It is possible that you will find that you have not much to do. If your IVD has FDA 510(k) clearance, you will already have most of the clinical and performance data needed for the PER. If you have a Quality Management System in place that complies with ISO 13485, you will not need many changes to comply with Annex IX. Compare the Essential Requirements from the IVDD with the GSPR of the IVDR and determine what additional tests and documentation you need.
3. **Prepare a plan of action**
   Now that you know where your gaps are, prepare a transition plan for your products, according to the IVDR transition timeline. You will need to consider how long your IVDD CE certificates will remain valid and if it makes sense to try to renew them or transition to the IVDR sooner. Once you decide when to transition to the IVDR, determine what additional tests your device will require. Since many more IVDs will require additional testing and NB oversight, there will be a lot of demand for NB resources and reference labs, so plan accordingly.
4. **Fill those gaps**
   Once your plan is in place, assign responsibilities and resources to deal with the workload to fill the gaps. Determine if you will need to hire extra staff or external consulting help. If you do not have a QMS in compliance with ISO 13485 in place, get one ASAP. Start gathering the necessary technical documentation and plan your clinical and performance studies.
5. **Get your EOs (and PRRC) on board**
   Make sure your EOs and PRRCs are aware of their new responsibilities according to the IVDR. Discuss with your importers, distributors and AR how they are preparing for the IVDR. Draw up new contracts and find new suppliers if needed. It is the manufacturer's responsibility to make sure that the EOs assume these new obligations.

Conclusion

The IVDR was introduced to address the shortcomings of the IVDD, which has become increasingly inadequate in world with rapidly advancing medical diagnostics technology. It brings regulations regarding IVDs closer in line with international regulations, such as the FDA, and guidances. The IVDR is a regulation and therefore EU member states must apply it in their national law.

IVD manufacturers will have to seriously consider the implications of the IVDR and the new obligations placed on them. They may find that for some products, it is not financially beneficial to make the transition and it is better to scrap them.

While the task of moving to the IVDR may seem daunting, it is important to understand the reasoning behind it. Safety of the individual and the public should always be the number one priority in healthcare and medicine. Remember that when you or a family member receive medical care, you want it to be at the highest standard. Make sure your IVD meets the standards you would expect for yourself and your loved ones.

Li-Med can help

Li-Med supports medical device and IVD manufacturers overcome regulatory hurdles.

We can help with:

- *IVDD to IVDR Gap Assessment*
- *IVD classification and conformity assessment*
- *Technical Documentation and PER preparation*
- *Quality Management (ISO 13485:2016 and QSR)*
- *PRRC services*

Contact us at office@li-med.com for further information.