IVDR and LDTs: How to prepare your lab for IVDR?

A practical approach

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Background Jeanine Kruijsbeek

After her traineeship at the Women's and Children's Hospital in Adelaide, South Australia, Jeanine started her career working as a medical laboratory analyst at the laboratory for Clinical Chemistry of Ziekenhuis Amstelland. At an early stage she was interested in standardizing and improving laboratory processes and in 2001 became a quality manager. In 2010 she joined the Kerteza team where she works as a senior consultant and trainer. As a consultant she advises hospitals and medical laboratories on how to implement and improve quality management systems. She actively participates in the Dutch NEN-IVD committee and the international ISO/TC 212. Over the years Jeanine developed a passion for simplifying quality management systems in health care and related regulations/ standards.

In this article Jeanine gives her practice based views on implementation of the IVDR for LDTs.

Key concepts IVDR

When you read the IVDR[1] front to back you could summarize the IVDR in a couple of key concepts that reflect the intent of the IVDR. These key concepts can guide you when implementing the IVDR.

Box 1. Key concepts IVDR

To guarantee **reliable** diagnostics that are fit for their **intended use** we need **competent professionals** who know the risks that might have an effect on **patient outcome and safety**. These professionals take **responsibility** for their actions. They are **proactive** and they consider the **ethical implications** of their decisions. They give **evidence** on why and how they do what they do.

The inside out© approach

The biggest pitfall when implementing the IVDR is starting with the question: 'What do I need to do to comply with this regulation/ standard?'. The alternative approach, starting from the 'inside out' starts with the question 'What do I need to do to guarantee reliable patient outcome and patient safety?'. This approach will give you several benefits. You stay focussed on your intention, your purpose. By keeping this focus you will do those things that add value to this purpose. This is not only efficient and more effective, but this way professionals feel more engaged and more in control of their work.

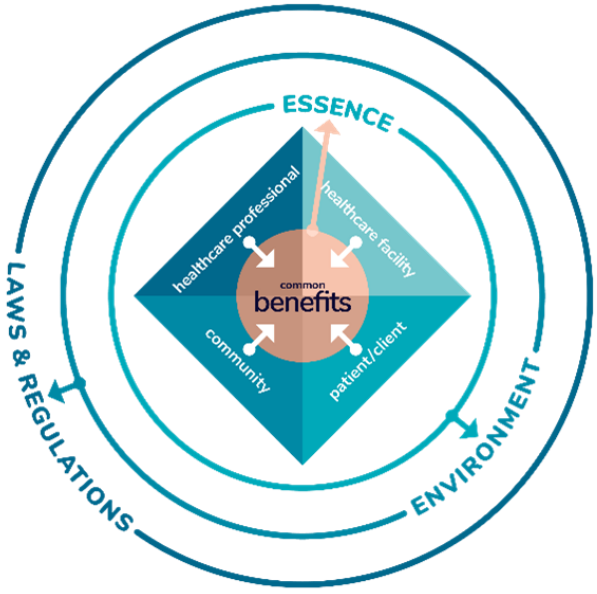

Figure 1. Kerteza Inside out model®

Preparing yourself

Stay informed

You need knowledge and insights to be able to implement the IVDR. Find out which information resources give reliable information on the IVDR and on specific components of the IVDR, e.g. performance evaluation. The Medical Device Coordination Group (MDCG) develops guidance documents on several relevant topics, including laboratory developed tests. The ISO technical committee TC 212 has formed a preliminary working group with the objective to write guidance for the use of LDTs. The abstract of the 8th ESLHO conference[2] gives a comprehensive overview of the articles of the IVDR that are relevant for LDTs.

Box 2 Information resources:

- European Commission
  - Medical Device Coordination Group (MDCG)
  - European Committee for Standardization (CEN)
  - CEN/TC 140 In vitro diagnostic medical devices
- National Governmental authorities
  - Health Care Inspection
  - National Accreditation Body
  - National Standardization Body
- International Standardization
  - ISO/TC212: preliminary working group to write guidance on LDTs

Know the playing field

There are a lot of players on the field. And although the mutual interest is patient safety, everyone has his own interest, role and responsibility in the implementation process.

Make sure you know who is playing which role, what your responsibility is and how you can influence the process.

Figure 2. Actors on the IVDR playing field

Medical laboratory professionals can play an important role in translating the IVDR to practice. The European Commission, the MDCG, CEN and ISO need the input of medical professionals to be able to define suitable requirements and guidance that guarantee patient safety and that are also practical and do not lead to overregulating the market.

Regarding LDTs the Notified Bodies and manufacturers play an indirect role. When notified body capacity is scarce the effect might be that manufactures cannot get their current IVDs CE-labelled which might lead to unavailability of CE-IVDs. This might trigger the need for laboratories to develop LDTs. Quit a lot of 'if's', but important to keep yourself informed on the current situation.

Keep informed on what your national authorities are doing to guide the implementation of the IVDR. We see differences in how the European member states are going about this process. It will be interesting to see what value different European member states will give to an ISO15189 accreditation in relation to proving compliance with the IVDR and in relation with oversight by the Health Inspections.

When we talk about risks to patient safety in relation to regulation we automatically need to consider the subject of liability. Hopefully this will not be a big issue, but it might be wise to get in contact with your legal department and insurance company to find out their point of view on this topic.

The medical laboratory needs to provide the conditions to be able to comply with the IVDR. The role of the medical laboratory professionals is outlined in Box 1 of this article. Clinicians and patients, although the latter indirectly, play an important role in providing feedback on their experience with the LDT and it's fitness for the intended use and clinical need.

Getting to work: a practical approach

- Step 1 Make an assay inventory

When we talk about LDTs we mean:

1. assays completely developed by the laboratory (*de novo*)
2. CE-IVD labelled assays used for a different intended use
3. CE-IVD labelled assays modified for your intended use or your specifications
4. Research Use Only (RUO) assays used as a diagnostic assay

While making this inventory also (try to) get information from manufactures on which CE-IVD labelled tests will and will not stay on the market.

- Step 2 Decide on your assay portfolio

Based on the inventory you can decide which assays you want to keep as part of your portfolio. Discussing the clinical need of certain assays should be part of the decision process, this will also help you to justify the need for the a LDT.

- Step 3 Justify the need for the LDT

The IVDR requires that all IVDs comply with the IVDR with the exception of LDTs taking into account the specified conditions in article 5.5 and the requirements of Annex I. LDTs are only allowed when 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. The Dutch IVDR Taskforce describes in their guidance document[3] aspects that can provide justification for the need for a LDT.

- Step 4 Determine the GAP: QMS versus IVDR

A quality management system (QMS) secures all the processes needed to guarantee reliable patient outcome and safety. When you have based your QMS on ISO15189 you should have processes in place that correspond with the requirements from the IVDR and can serve as a framework to prove compliance with the IVDR.

But at present the ISO15189:2012 is not a harmonised standard. So you will have to convince your national authorities and show evidence that complying with ISO15189 is sufficient to prove compliance with the relevant parts of the IVDR. ISO15189 tells you *what* to do, but does not tell you *how* to perform your work. The ‘how’ is, and should be, the responsibility of competent medical professionals.

The amount of actions needed to adapt your QMS depends on how you have organised certain aspects of your QMS. Experience with implementing the IVDR for LDTs learns that there might be a gap in your QMS in these four fields:

- Risk management per assay during the whole life cycle of the assay

  Most laboratories have implemented risk management on a process level and not explicitly on an assay level. The good news is that your validation plan is also a type of risk management plan. Adapting your validation procedure based on the relevant aspects of the IVDR will help you to comply with the relevant parts of chapter 1 of Annex I.

  Ideally you embed risk management of the LDTs in a risk management framework that is applicable to your whole organisation and processes.

Box 3. Risk management standards

- ISO 31000:2018 Risk management (organisation level)
- ISO 22367:2020 Risk management. Medical laboratory (process level)
- ISO 14971:2019 Risk management Medical Device (device level).

- Performance evaluation

  Chapter VI, article 56 – 58 and Annex XIII describe requirements related to clinical evidence, performance evaluation and performance studies. The evaluation of the performance consist of scientific validity and analytical and clinical performance. As a medical laboratory professional you know what is necessary to validate an assay.

  Field observations show that there are differences between medical laboratory disciplines in their experience with validating assays (e.g. Clinical Chemistry, Anatomical Pathology and Medical Microbiology) Interesting questions to answer are:

  - Does your current validation procedure cover the relevant aspects to be able to give evidence of the performance of the LDT?
  - Do the technical aspects of laboratory medicine, e.g. performance evaluation, get enough attention in the curriculum of the study program of medical laboratory professionals?
  - Do we make use of all the relevant knowledge and insights available on performance evaluation?

- Post market surveillance

Post-market surveillance, vigilance and market surveillance is covered by Chapter VII, article 78 and 82 of the IVDR. You will have to setup a post-market surveillance system that is in line with the risks related to the assay and is part of the quality management system. It gives you information on the quality, performance and safety of the LDT. When your QMS is based on ISO15189:2012 you already have processes in place that generate the required information.

- Technical documentation.

Chapter III of Annex I gives detailed requirements on information that should be supplied with the device. You will find these requirements are mostly applicable to manufactures of CE-IVDs and have a limited application for LDTs. Concerning documentation you will need to give most of your attention to giving evidence of compliance with the relevant parts of Annex I.

- Step 5 Adapt your QMS as needed

You can make an implementation plan based on your assay portfolio and the gap analysis of the QMS. Make use of the relevant processes of the QMS that are already in place.

- Step 6 Show evidence

One of the responsibilities of the laboratory is to document information that:

  - justifies the need for the LDT (see step 3)
  - shows evidence of the performance (life cycle)
  - shows compliance with relevant parts of Annex I of the IVDR

The information on performance of the LDT is mostly generated during the validation process and the post-market surveillance and will be part of the quality management system. You might want to structure this information to guarantee that it is readily available on inspection. Compiling an assay portfolio for this purpose is recommended. Adding an annex to the validation procedure and/ or the validation report can be useful to show compliance with relevant parts of Annex I of the IVDR.

Box 4. Post-market surveillance and ISO15189:2012

- Quality control programs (internal and external quality control)
- Quality indicators
- Non-conformity assessments
- Feedback of users
- Other evaluation instruments, e.g. audits and management reviews

Take home messages

- Start from the inside out: patient outcome and safety.
- Learn as much as you can about the IVDR.
- Know the playing field and how to influence it.
- Get involved on a national, European and international level.
- Follow a step by step, risk based, approach when implementing the IVDR.
- Use the key concepts of the IVDR when implementing the IVDR (Box 1).

References

1. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0746
2. Bart B Lubbers et al. How to prepare for the IVDR? Practical information and concrete actions for diagnostic laboratories and consortia. Abstract 8th ESLHO symposium 2019.
3. Jacobs LHJ et al. Guidance on use of Lab-Developed Tests as described in REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on in vitro diagnostic medical devices, Task force IVDR Draft version V0.1.1 11-09-2020.