Regulatory Requirements for the Use of In-House Tests / Laboratory-Developed Tests under the IVD Regulation (EU) 2017/746

With the entry into force of the EU In Vitro Diagnostics Regulation 2017/746 (IVDR), self-developed IVD tests, also called laboratory-developed or in-house tests (LDTs), have received a boost in attention. This is because, unlike the IVD Directive, the IVDR provides a more detailed regulatory framework for the manufacture and use of LDTs. This position paper explains the new framework and what requirements apply to LDTs.

This position paper does not constitute legal advice. It provides an interpretation and explanations of IVDR requirements for LDTs from the author's perspective.

1. Which IVD tests are considered “in-house tests” (IHT) or “laboratory-developed tests” (LDTs), respectively?

Laboratory-developed tests are *in vitro* diagnostic tests that are developed, manufactured, and used in a health institution (HI). These tests employ components (reagents, kits, controls, devices, software) without CE-IVD labelling or rely on a combination of CE and non-CE labelled components for *in vitro* diagnostic purposes. However, the use of an approved CE-IVD product outside of its intended purpose also falls into the category of LDTs or IHTs.

In most cases, LDTs are often niche products for the diagnosis of rare diseases for which no adequate commercial diagnostic is available. But they may also comprise of innovative test methods that are not yet used in commercially available IVD products. Regardless of the individual constellation, LDTs serve to close gaps in the healthcare system and improve the therapy of certain patients.

2. How are LDTs regulated by law?

Since LDTs are *in vitro* diagnostic devices, they are in general within the scope of the IVD Medical Device Regulation (EU) 2017/746 (IVDR). Unlike under the IVD Directive 98/79/EC, the requirements for the use of LDTs are specifically mentioned in Article 5(5) of the IVDR. The legislators saw a need to provide a better framework for the manufacture and use of *in vitro* diagnostic LDTs regarding the control of their safety and performance. This is reflected in the preface of the IVDR, where point 28 states: ”To ensure the highest level of health protection, the rules governing IVD medical devices, manufactured and used within a single health institution only, should be clarified and strengthened.”

The IVDR therefore provides special provisions for LDTs. They may not be placed on the market but must be manufactured and used only at the same health institution. This HI must be established in the European Union. A transfer to other health institutions such as laboratories or healthcare facilities is not permitted. This also applies to subsidiaries of a health institution if those represent legally independent entities.

3. What requirements must be considered for using LDTs?

Article 5 (5) of the IVDR regulates precisely when an LDT may be used as such. If all these conditions are met, the LDT in question is exempt from many of the requirements of the IVDR. For example, it does not have to undergo a conformity assessment procedure, as is required for commercial CE-IVD products and manufacturers. Therefore, the LDT must not be marked with a "CE" either. Nevertheless, the operating HI must ensure that the General Safety and Performance Requirements (GSPR) as specified in Annex I of the IVDR are met and fulfilled by the LDT. This is confirmed by the issuance of a legally binding and publicly available declaration by the HI.

4. What exactly do these requirements for the use of LDTs include? How can I meet them and from when are they to be complied with?

The following paragraphs explain the requirements specified in Article 5 (5) in more detail. With Regulation (EU) 2022/112, the legislators have granted an extended transition period for almost all requirements in order not to jeopardize patient care. Only point (a) must already be complied with since 26th May 2022. Point (d) has to be considered and complied with until from 26th May 2028. All other points will enter into force by 26th May 2024.

a) The devices are not transferred to another legal entity.

See also Question 2. This is important, because otherwise the device is considered been made available on the market.

b) Manufacture and use of the devices occur under appropriate quality management systems (QMS).

The defined manufacturing process as well as the testing procedure must be validated and evaluated on a risk basis.

The health institution acts as a manufacturer as well as a user of its own *in vitro* diagnostics (reagents, kits, devices, software). All applicable activities must be considered and regulated in the QMS. Risk management, change control and monitoring of processes for the evaluation of measurement results are already implemented in the requirements of ISO 15189. However, written regulations for development and manufacturing may be missing in the laboratory’s QMS. The most important points are:

i. **Control of production.** This refers to the following requirements to be met: preparation and use of version-controlled manufacturing instructions; qualification of the production facility and equipment used; monitoring and measurement of processes and results (quality controls); use of appropriate and regularly maintained measurement equipment; accurate documentation of the production of the devices.
ii. **Cleanliness of devices.** They must be clean and free of residues that may affect the function or shelf life of the devices.
iii. **Validation of manufacturing processes.** If the results of a manufacturing process cannot be 100% verified, a validation must demonstrate that (a) the process produces reproducible results and (b) that product quality control on a sampling basis is sufficient.
iv. **Identification and traceability.** Device batches produced must be clearly identifiable at any time and the manufacturing documents (see point i) must allow traceability of the diagnostic results not only back to the sample but also to the raw materials used for device manufacturing.

c) **The laboratory of the health institution is compliant with standard EN ISO 15189 or where applicable to national provisions, including national provisions regarding accreditation.**

This requirement is fulfilled if the work of the laboratory is accredited according to EN ISO 15189 or complies with respective national guidelines, such as those of the German Medical Association (RiliBÄK). Please consult local stake holder organisations in your country for information, which national guideline or provision is accepted for showing compliance to IVDR requirements in your country.

d) **The HI 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 [CE-IVD certified] device available on the market.**

The wording of Article 5 clearly points to the fact that economic factors such as product price cannot be considered a reason for avoiding the use of a CE-IVD certified device. Acceptable circumstances for using LDTs, however, may be insufficient analytical or clinical performance of existing CE-IVD certified devices for the specific intended purpose. Furthermore, the lack of availability of CE-certified devices could also justify why in-house alternatives must be used. At this point, it should be mentioned again that a justification for the use of an LDT is only required by May 2028.

e) **The HI 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.**

This point should be seen in conjunction with point (g). The required information can be summarized as a product file. Depending on local law and the risk class of the device, you may be obliged to provide detailed and specific information for Class D devices only, or for devices of all risk classes. In Germany, for example, the legislators require the product files of all LDT devices (independent of their risk class) to contain the following information: Intended purpose, manufacturing site and process including raw materials, design information (test principle, design, application, labelling and instructions for use), performance data (analytical, clinical), compliance with applicable safety & performance requirements according to Annex I of the IVDR. The German AWMF has created a compact template for this purpose, which can be downloaded from their website.
I recommend reviewing the legal situation in your country and to check if there are templates for product files available from stake holder organisations in your country.

f) **The HI draws up a declaration that the LDT device meets the General Safety and Performance Requirements (GSPR) laid down in Annex I of the IVDR.**

The declaration must provide specific information on the HI and the device itself. Again, a template is available from the German AWMF. You may want to check if there are similar templates available from organisations in your country.

g) **As regards class D devices […], the HI draws up documentation that makes it possible to have an understanding of the manufacturing facility, the manufacturing process, and the design and performance data of the devices including the intended purpose. The documentation must be sufficiently detailed to enable the competent authority to ascertain the GSPR set out in Annex I are met. Member states may apply this provision also to Class A, B or C devices.**

Details on the content of the product file have already been described in point (e). The product file must include a document showing which GSPRs are applicable to the LDT and how they have been met. More detailed information on this is provided in question 6. The product file as well as the public declaration must be archived for at least 10 years after the LDT has ceased to be used.

In the case of class D products, the requirements of the "Common Specifications" (EU) 2022/1107 must be taken into account during product validation. These include minimum requirements on the performance characteristics to be achieved and on minimum sample numbers for the clinical validation. The document can be downloaded here: https://eur-lex.europa.eu/eli/reg_impl/2022/1107/oj.

h) The HI takes all necessary measures to ensure that all devices are manufactured in accordance with the documentation referred to in point (g).

This requires a controlled manufacturing as explained in point (b).

i) The HI reviews experience gained from clinical use of the devices and takes all necessary corrective actions.

This condition corresponds to a continuous monitoring of the LDT's performance after the first "putting into operation". If deficiencies or complaints related to performance occur in everyday clinical practice, corrective and preventive actions must be initiated. Among other things, these may consist of checking whether changes are required, e.g., to the design, handling, manufacture or intended purpose. If this is the case, the changes must be implemented and documented as part of a defined change management process.

5. Which IVD devices fall into Class D?

With the implementation of the IVDR, the IVDD list system for risk classification of IVD tests was replaced by a flexible and sustainable classification system. The document MDCG 2020-16 of the *Medical Device Coordination Group* provides a good guidance on the classification of IVD tests including numerous examples. It is recommended to briefly review this document.

Tests of the highest risk class D include among others:

- Devices for blood grouping and for the determination of tissue markers if they are intended to be used for testing immunological compatibility in preparation for transfusion and transplantation.
- Devices for detection of transmissible pathogens in blood, cells, and tissues for determination of their suitability for transfusion, transplantation, or cell therapy (HIV, HBV, HCV, Treponema, Malaria, HTLV, CMV, EBV, Trypanosoma, Toxoplasma).
- Devices for detection of transmissible, life-threatening pathogens with a high risk of transmission (HIV, HBV, HCV, haemorrhagic fever viruses, HTLV, SARS-CoV-2, pandemic influenza strains, variola viruses).
- Devices for determination of the number of pathogens of life-threatening diseases when monitoring is critical for patient management.

6. What is covered by the General Safety and Performance Requirements?

The GSPRs are defined in Annex I of the IVDR. They include a variety of items to be met depending on the type of the IVD test, if applicable. The table below provides an overview of the GSPRs and guidance on how they can be met:

I. General Requirements	
Device shall achieve performance as intended by manufacturer	Achievement of the intended purpose is demonstrated by the results of the performance validation
Device shall be state of the art	Comparison of device performance with data in peer-reviewed literature or performance data of other CE-IVD devices with same intended purpose
Device shall be safe in use An active risk management (RM) system shall be implemented	Safety requirements towards patient and user must be met Implementation of a RM system for medical laboratories according to EN ISO 22367:2020 is recommended. Design and development activities are defined in Annex A.4. This standard emphasizes a risk-based development and provides specific guidance for implementation.

A RM plan shall be drawn up and device performance shall be continuously monitored to minimize risks arising from the use of the device	A product-specific risk analysis must be planned and established, which determines, evaluates, and assesses the effects of device defects as well as malfunctions on the LDT or the examination procedure and thus on the diagnostic results. Specific measures for risk reduction must be defined. Finally, a risk-benefit assessment must be conducted for the operation of the LDT with reference to the user and patient.
Performance shall be ensured over the full lifetime (shelf-life) of the device	The stability of in-house manufactured reagents must be determined experimentally (shelf-life study). For purchased components, reference can be made to the manufacturer's instructions.
II. Requirements regarding performance, design, and manufacture:	
Performance characteristics	The scientific validity of the biomarker of choice shall be verified. The analytical performance and clinical performance (if applicable) shall be determined. This also includes the influence of different sample types as well as endogenous and exogenous interferences, e.g., cross-reactions and inhibitors. In this regard, point 5.5.1 of EN ISO 15189 and applicable national quality assurance guidelines (such as the German RiliBÄK) provide valuable input regarding quality assurance and the state of the art of the LDT. The latter describe performance parameters, known interferences and detection limits as well as validation, verification & quality assurance of test methods by means of characterized reference samples, control and calibration material, reference measurement methods, shelf life and stability tests. This also applies to devices that are combined with or connected to other medical devices or equipment to fulfil their intended purpose as an LDT. The combination must not impair the intended performance of the devices. The intended purpose and the design of the combination of devices must be reviewed in a risk-based manner for medical diagnostic application.
Chemical, physical, and biological properties and related risks	Examine applicability on a case-by-case basis. Product information incl. safety data sheets from suppliers provide information on potential hazards.
Control of infectiousness and microbial contamination of devices containing materials of biological origin	Examine applicability on a case-by-case basis. Product information incl. batch analysis certificates from suppliers provide information on potential hazards. In case of doubt, more information can be requested from the supplier, how they ensure that the reagents are not infectious.
Construction, manufacture and interaction with the environment and related risks	Examine applicability on a case-by-case basis. Special attention should be given to the interaction of components (reagents, hardware, software). If applicable, this should be considered in the work instruction for the LDT device.
Devices with a measuring function	Examine applicability on a case-by-case basis.
Protection against radiation	Examine applicability on a case-by-case basis.
Programable electronic systems incl. software and related risks	Examine applicability on a case-by-case basis. If in-house developed code or software (programs, macros, data analysis algorithms) is used, these shall be version-controlled, and their functionality shall be validated prior to use. If applicable, these topics shall be discussed and reviewed in the risk assessment for the LDT and including the result reporting.
Devices with external or internal energy source and related risks	Examine applicability on a case-by-case basis. When using commercially available electric equipment, it can be assumed that all requirements are met by the equipment manufacturer. In case of doubt, a written statement can be requested from the manufacturer.
Protection against mechanical and thermal risks	Examine applicability on a case-by-case basis. When using commercially available electric equipment, it can be assumed that all requirements are met by the equipment manufacturer – see instructions for use. In case of doubt, a written statement can be requested from the manufacturer.
III. Requirements regarding information supplied with the device	
General requirements regarding supplied information	The requirements on the labelling of the LDT and its instructions for use (work instructions, SOP) are to be met.
Information on the packaging	Clear labelling of LDTs and semi-finished products from the manufacturing process including shelf-life, batch information and hazard information. Traceability must be ensured at any time and at any point of the manufacture and use of the LDT device.
Information in the instructions for use	Description and information in the work instruction for the LDT including form sheet for data and result recording. The SOP should provide guidance on sample quality and sample preparation as well as endogenous & exogenous interferences.

7. Which IVDR requirements for quality, risk and change management are met by EN ISO 15189?

Health institutions often operate under a QM system accredited in accordance with EN ISO 15189. Thus, they are well prepared for the IVDR. It is important to understand that the IVDR only defines requirements for the development, manufacture, performance monitoring and safety reporting of IVDs. IVDR does not contain any requirements for quality assurance during the use of IVDs.

Here is how EN ISO 15189 covers all relevant topics for the use and application of IVDs (including LDTs):

PROCUREMENT: Products to be procured (CE-IVD as well as non-IVD) and all materials used in the diagnostic procedure are subject to incoming inspection and release testing, which enable the traceability of diagnostic results via the test reagents to the respective starting materials.

VALIDATION: Before implementation, the performance claims of the diagnostic procedure are verified to fulfil the intended purpose of the LDT, the procedure is validated, and the results are evaluated regarding the performance characteristics on a risk basis. In-house developed software, spread sheet scripts, or evaluation sheets must also be validated. After approval, the diagnostic method is ready for routine use.

RISK MANAGEMENT: EN ISO 15189 provides detailed specifications regarding quality requirements for the IVD devices used, the handling of patient samples, the examination procedures used, the evaluation and release of results. Thus, large parts for an active risk and change management are fulfilled. Nevertheless, a look at the actual RM standard for medical laboratories EN ISO 22367 is recommended. This standard provides valuable input to ensure a systematic risk analysis and the definition of risk-reducing measures. The evaluation of potential interferences reviews their effects on procedures, on product and sample stabilities and, thus, on the diagnostic results. Risk mitigation measures for patient and user may require changes to the product or the diagnostic procedure and sometimes also to the QM processes.

CHANGES / CORRECTIVE ACTIONS: Changes may occur for various reasons, e.g., operational issues that result in corrective actions. Any changes must pass a defined review and approval process with verification, validation, and risk assessment stages. It should also be reviewed whether preventive measures can be taken to avoid similar errors in other areas.

QUALITY CONTROLS: The diagnostic procedures are subject to daily quality controls using defined control materials for quality assurance purposes. Infrastructure, equipment, and measuring devices are always qualified within test plans and metrological traceability is always provided. Procured reagents and consumables are subject to incoming inspection and are tested upon receipt for release to the laboratory. Process descriptions and work instructions are available for routine use by trained operators with information on potential error modes. This includes processes for pre-analytical measures, examination procedures and for post-analysis to ensure proper quality of released diagnostic results.

MONITORING OF PRODUCT: Experience gained from the use of LDTs must be assessed in accordance with the IVDR and the performance of the devices shall be continuously evaluated. Through internal quality controls as well as external quality assessment programs, the performance characteristics of the LDT devices are continuously assessed and reviewed. That way, hazards and hazardous situations can be identified at an early stage and appropriate protective and mitigating measures can be taken. Based on these measures, LDTs are monitored throughout their entire life cycle and the regulatory requirements of IVDR Article 5(5) are met.

REPORTING: Experiences from routine diagnostic use of LDTs are collected and recorded by a complaint management and feedback system the staff and customers of the laboratory. The gathered data are regularly analysed and evaluated to enable prompt reaction to trends or deviations. A serious incident reporting and safety corrective action process shall be in place, which ensures reporting to the responsible regulatory authority.

8. How do I prepare my QMS for the development and production of LDTs?

It is recommended to operate a QM system according to EN ISO 15189. Yet, while this ISO standard is very well suited for controlling the operational use of IVD products (see question 7), it lacks specifications for product development and manufacturing. To close this gap to the additional IVDR requirements, it is recommended to implement the provisions of the risk management standard EN ISO 22367. It covers all phases of a LDT's life cycle from the design up to the diagnostic results and complements EN ISO 15189 in aspects of development and manufacturing. In fact, both standards are linked via control measures between quality management and risk management.

Point 4 of Annex A of EN ISO 22367 describes the design and development phases up to the validation of manufacturing and testing procedures for the qualification of LDTs including risk-based verification and approval activities. The specifications are based on the requirements of EN ISO 13485 but are tailored to the requirements of medical laboratories.

SUMMARY

Laboratory-developed tests (LDTs) may continue to be developed and manufactured for in-house use at health institutions (HI) if the requirements of IVDR Article 5(5) are met. Since the HI is not required to conduct a conformity assessment procedure for the LDT, the IVD must not be “CE” marked. The LDT is put into service for self use without assessment by a Notified Body, regardless of the risk class. The documentation of the LDTs as required by the IVDR in Article 5 must be kept available for review by the competent authority.

From May 2024, in-house production, modification, and use must be conducted under a suitable quality management system (QMS). The QMS should be set up in conformity with the requirements of EN ISO 15189. The risk management standard EN ISO 22367 (in particular Annex A) provides good guidance on how to meet additional requirements for LDT-manufacturing HIs. The latter standard provides guidance for risk assessment for the design of LDTs and their manufacturing processes in order to meet the General Safety and Performance Requirements of IVDR Annex I. Ideally, national quality assurance guidelines support the QM system with specifications for performance characteristics and measurement methods that reflect the current state of the art, as well as with specifications for internal and external quality assurance. Records on the manufacturing site, manufacturing processes, intended purpose, design and performance data should be summarized in a product file together with risk-based assessments derived from verification, validation, and approval activities to demonstrate compliance in accordance with IVDR Article 5(5). This product file must be made available to local authority. From May 2028, the HI has to justify that there is no at least equivalent CE-certified IVD product on the market.

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