Lab-Developed Tests

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

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1. Scope

The new European IVDR legislation will come into effect in May 2022. This may have major consequences for the use, availability and costs of in vitro diagnostic tests. To meet some of the potential challenges, the scientific societies of the (medical) laboratory specialists (in the Netherlands) have joined forces in a multidisciplinary task force. This task force consists of mandated members of the NVKC, NVVP, NVMM, VKGL / VKGN, NVVI / CMI and the NVZA.

In this document we will discuss the development and use of in vitro diagnostic tests developed in-house (lab developed tests [LDTs]), as described in regulation 2017/746 article 5, paragraph 5 of the IVDR. No rights can be derived (at this stage) from this document.

When in this document reference is made to an LDT this means the following:

- An in-house developed and produced test;
- Tests that are labeled "research use only" and that are used for diagnostics;
- A CE-certified test in which adjustments are made.

Note that under these definitions, any modifications to a CE-certified IVD will result in the IVD being labeled as an LDT. When adjustments are made to a CE-certified test, responsibility for the adjusted part of the IVD shifts from the manufacturer to the laboratory (see section 5e). There are exceptions for which it is not reasonably possible to comply with IVDR. These exceptions will generally relate to incidental, ad hoc modifications, usually necessary to answer an urgent clinical question. For example:

- Reporting results in the presence of an interfering substance.
- Measuring the analyte in a body fluid other than described (and certified) by the manufacturer.

In such cases, it is important to report (with the result) that the specific measurement was generated with a non-validated analysis and lies outside of the EN ISO 15189 accreditation.

The law states that LDTs may only be applied on a non-industrial scale: An exact definition of “industrial scale” is lacking in the IVDR. In a general sense, it is the view of the task force that tests developed in-house, which are used for patient care, are not applied on an industrial scale.

2. Target audience

The guidance is written for employees of health institutions, health care professionals and researchers, who aim to continue the use of LDTs or to set up new LDTs.

3. Explanatory notes Chapter II, article 5, paragraph 5

"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:"

Annex I contains a number of important general requirements that are set for the safety and performance of IVDs. In our opinion, these requirements represent a significant improvement of current legislation and are in line with the stringent quality requirements set out and met by most medical laboratories in the Netherlands (see also the report of the National Institute for Public Health and the Environment: https://www.rivm.nl/publicaties/in-huis-ontwikkelde-ivd-testen-gebruik-en-kwaliteitsborging).

In particular, there is a large degree of overlap between the requirements set in EN ISO 15189 and those listed in Annex I. Therefore, in-house tests, which are developed and validated in EN ISO 15189 accredited laboratories will, for the most part, comply with Annex I of the IVDR.

To illustrate that most of the requirements in Annex 1 are safeguarded by the EN ISO 15189 accreditation we have cross-referenced, in appendix A, all of the requirements in Annex 1 to those in the EN ISO 15189 standard. Appendix A is therefore also a practical tool for laboratories to demonstrate that they comply with the requirements set out in Annex I.

Note that this only applies to laboratories/IVD-tests that are accredited according to EN ISO 15189.

5a) the devices are not transferred to another legal entity;

It is permissible, and often essential for the quality and accessibility of our healthcare system, that test results and corresponding analytical or clinical interpretations (if applicable) can be shared with referring healthcare providers. The LDTs cannot be transferred to other legal entities, the results produced with the LTDs can.

Sharing relevant protocols, work instructions and clinical validations with colleagues in other institutions and describing LDTs in scientific publications is allowed.

5b) manufacture and use of the devices occur under appropriate quality management systems;

In general, the quality management system under EN ISO 15189 can be seen as an appropriate quality management system. Nonetheless, there is a considerable heterogeneity in manufacturing processes and we cannot exclude the possibility of additional requirements.

5c) the laboratory of the health institution is compliant with standard EN ISO 15189 or where applicable national provisions, including national provisions regarding accreditation;

Being EN ISO 15189 accredited is the most effective way to comply with this part of the law.

5d) 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;

The health institution must justify its use for each LDT. It will be necessary to demonstrate and prove that the specific needs of a patient group cannot be met, or cannot be met at the right performance level, by an equivalent (CE-certified) device available on the market.

Arguments that can be taken into consideration to demonstrate the necessity and superiority of the LDT:

Technical:

- Working principle
- Critical performance requirements
- Required amount of patient material
- Type of (body) material
- Reliability of the device
- Turn-around times
- Clinical compatibility and interdependent comparison of results from the same material (taken at the same time). For example: a multiplex assay can measure multiple parameters simultaneously in one analysis, instead of several independent tests.

Clinical:

- Is the device used for the same clinical condition or the same goal? E.g.:
    - The same severity and stage of the disease
    - In the same place in the body
    - In a comparable population, including age, anatomy and physiology
    - How do the relevant critical performances compare in view of the expected clinical effect for a specific intended purpose?

Substantiation of the above can be based on (but is not limited to):

- National guidelines from professional associations / international guidelines
- Scientific literature
- Expert opinion e.g. clinical utility cards

Clarification:

The argumentation should make clear that the LDT is necessary to meet a specific need. This need should concern a relevant and clinical benefit for the patient; The Dutch ministry of health (VWS) and our competent authority (IGJ) have indicated that financial considerations do not justify the use of LDTs.

The IVDR does not specify when the lack of an alternative for the device must be justified. An appropriate moment is at the start of the LDT's development process, when the functional requirements and the patient target group are known. Subsequently, a re-assessment will have to be performed at the end of the life cycle of the LDT or when the LDT is changed. For medical devices (LDTs) that are produced without a clear (end of) life cycle or that are not subject to change, market orientation needs to be performed at a reasonable frequency to check for the availability of equivalent, commercially available alternatives. The information published in EUDAMED is leading for this.

5e) 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;

All previously mentioned items must be documented and be made available upon request of the competent authorities.

In case of minor modifications to a certified test that improve the function of the test or increase the scope of application, it is important to make a risk analysis of the implications of the modification on the performance characteristics of the test. In addition, the modification will need to be validated, thereby focusing on the performance characteristics that are reasonably affected by the modification. Examples of limited modifications:

- Inclusion of a factor (e.g. + 10%) to harmonize the results with those in other laboratories
- Making a dilution
- The use of other body material, for example COVID-19 test on bronchoalveolar lavage fluid (where the test describes, for example, only use of nasal swabs)

For performance characteristics not affected by the modification, the laboratory can refer to the manufacturer's documentation. When adjustments are made to an IVD, responsibility for the adjusted part of the IVD shifts from the manufacturer to the laboratory.

5f) 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 therefor;

An example is supplied in appendix B. The filled in declaration can be made public on the website of the healthcare institution.

5g) as regards class D devices in accordance with the rules set out in Annex VIII, the health institution draws up documentation that makes it possible to have an understanding of the manufacturing facility, the manufacturing process, the design and performance data of the devices, including the intended purpose, and that is sufficiently detailed to enable the competent authority to ascertain that the general safety and performance requirements set out in Annex I to this Regulation are met. Member States may apply this provision also to class A, B or C devices in accordance with the rules set out in Annex VIII;

For the time being, we assume that this requirement only applies to class D devices.

5h) the health institution takes all necessary measures to ensure that all devices are manufactured in accordance with the documentation referred to in point (g); and

(i) the health institution reviews experience gained from clinical use of the devices and takes all necessary corrective actions.

Again, EN ISO 15189 accreditation provides the required assurances, in particular on the basis of section 4.14 (Evaluation and Audits).

4. List of abbreviations

Abbreviation	Meaning
CE	Conformité Européenne
ISO	International Organization for Standardization
IVDR	In Vitro Diagnostic Regulation
LDT	Lab Developed Test

5. Attachments

5.1 Appendix A Cross-reference Annex I of REGULATION (EU) 2017/746 to EN ISO 15189

The overview below shows for each requirement of Annex I (IVDR 2017/746) which EN ISO 15189 element ensures the relevant part of the law. The task force has made this overview, based on professional considerations, to enable laboratories to provide insight into and further elaborate adherence to the IVDR. It is a practical handle from which no rights can be derived.

The following colors have been used in the overview below:

Reference to EN ISO 15189
Advice to comply with this part
Limited application, with advice to members
Not applicable

	Chapter 1: General safety and performance requirements	EN ISO 15189 / Remarks
1	Devices shall achieve the performance intended by their manufacturer and shall be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose. They shall be safe and effective and shall not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art.	EN ISO 15189 wide
2	The requirement in this Annex to reduce risks as far as possible means the reduction of risks as far as possible without adversely affecting the benefit-risk ratio.	4.14.6
3	Manufacturers shall establish, implement, document and maintain a risk management system. Risk management shall be understood as a continuous iterative process throughout the entire lifecycle of a device, requiring regular systematic updating. In carrying out risk management manufacturers shall:	EN ISO 15189 is a fully suitable risk management system with which you meet the requirement to document and maintain the quality and risks (iteratively) throughout the life of a device. section 4.14.6, in a broad sense 4.14 (with regard to evaluation and assurance), 4.12 and 4.15.1
a)	establish and document a risk management plan for each device;	
b)	identify and analyse the known and foreseeable hazards associated with each device;	
c)	estimate and evaluate the risks associated with, and occurring during, the intended use and during reasonably foreseeable misuse;	
d)	eliminate or control the risks referred to in point (c) in accordance with the requirements of Section 4;	
e)	evaluate the impact of information from the production phase and, in particular, from the post-market surveillance system, on hazards and the frequency of occurrence thereof, on estimates of their associated risks, as well as on the overall risk, benefit-risk ratio and risk acceptability; and	
f)	based on the evaluation of the impact of the information referred to in point (e), if necessary amend control measures in line with the requirements of Section 4.	Advice to members for Section 3: perform a risk analysis for each test
4	Risk control measures adopted by manufacturers for the design and manufacture of the devices shall conform to safety principles, taking account of the generally acknowledged state of the art. To reduce risks, the manufacturers shall manage risks so that the residual risk associated with each hazard as well as the overall residual risk is judged acceptable. In selecting the most appropriate solutions, manufacturers shall, in the following order of priority:	EN ISO 15189 is a fully suitable risk management system with which you meet the requirement to document and maintain the quality and risks (iteratively) throughout the life of a device. section 4.14.6, and in a broad sense 4.14 (with regard to evaluation and assurance)
a)	eliminate or reduce risks as far as possible through safe design and manufacture;	

	Chapter 1: General safety and performance requirements	EN ISO 15189 / Remarks
b)	where appropriate, take adequate protection measures, including alarms if necessary, in relation to risks that cannot be eliminated; and	
c)	provide information for safety (warnings/precautions/contra-indications) and, where appropriate, training to users.	Advice to members for Section 4: perform a risk analysis for each test
	Manufacturers shall inform users of any residual risks.	
5	In eliminating or reducing risks related to use error, the manufacturer shall:	
a)	reduce as far as possible the risks related to the ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety), and	5.2
b)	give consideration to the technical knowledge, experience, education, training and use environment, where applicable, and the medical and physical conditions of intended users (design for lay, professional, disabled or other users).	5.1.2; 5.1.6
6	The characteristics and performance of a device shall not be adversely affected to such a degree that the health or safety of the patient or the user and, where applicable, of other persons are compromised during the lifetime of the device, as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use and has been properly maintained in accordance with the manufacturer's instructions.	4.14.5; 4.14.7; 4.14.8; 5.6
7	Devices shall be designed, manufactured and packaged in such a way that their characteristics and performance during their intended use are not adversely affected during transport and storage, for example, through fluctuations of temperature and humidity, taking account of the instructions and information provided by the manufacturer.	5.2.3; 5.2.6; 5.3
8	All known and foreseeable risks, and any undesirable effects shall be minimised and be acceptable when weighed against the evaluated potential benefits to the patients and/or the user arising from the intended performance of the device during normal conditions of use.	EN ISO 15189 wide, especially 4.14.6

	Chapter 2: Requirements regarding design and manufacture	EN ISO 15189 / Remarks
9	**Performance characteristics**	
9.1	Devices shall be designed and manufactured in such a way that they are suitable for the purposes referred to in point (2) of Article 2, as specified by the manufacturer, and suitable with regard to the performance they are intended to achieve, taking account of the generally acknowledged state of the art. They shall achieve the performances, as stated by the manufacturer and in particular, where applicable:	5.5.1.3
a)	the analytical performance, such as, analytical sensitivity, analytical specificity, trueness (bias), precision (repeatability and reproducibility), accuracy (resulting from trueness and precision), limits of detection and quantitation, measuring range, linearity, cut-off, including determination of appropriate criteria for specimen collection and handling and control of known relevant endogenous and exogenous interference, cross-reactions; and	5.5.1.3; 5.5.1.4
b)	the clinical performance, such as diagnostic sensitivity, diagnostic specificity, positive predictive value, negative predictive value, likelihood ratio, expected values in normal and affected populations.	5.5.1; 5.5.2
9.2	The performance characteristics of the device shall be maintained during the lifetime of the device as indicated by the manufacturer.	5.6.2
9.3	Where the performance of devices depends on the use of calibrators and/or control materials, the metrological traceability of values assigned to calibrators and/or control materials shall be assured through suitable reference measurement procedures and/or suitable reference materials of a higher metrological order. Where available, metrological traceability of values assigned to calibrators and control materials shall be assured to certified reference materials or reference measurement procedures.	5.3.1.4; 5.5.1.4; 5.5.2
9.4	The characteristics and performances of the device shall be specifically checked in the event that they may be affected when the device is used for the intended use under normal conditions:	
a)	for devices for self-testing, performances obtained by laypersons;	Not applicable, LDTs are not for self-testing, because they should not be transferred
b)	for devices for near-patient testing, performances obtained in relevant environments (for example, patient home, emergency units, ambulances).	Not applicable, LDTs are not for near-patient testing, because they should not be transferred

	Chapter 2: Requirements regarding design and manufacture	EN ISO 15189 / Remarks
10	**Chemical, physical and biological properties**	
10.1	Devices shall be designed and manufactured in such a way as to ensure that the characteristics and performance requirements referred to in Chapter I are fulfilled. Particular attention shall be paid to the possibility of impairment of analytical performance due to physical and/or chemical incompatibility between the materials used and the specimens, analyte or marker to be detected (such as biological tissues, cells, body fluids and micro-organisms), taking account of the intended purpose of the device.v	5.5.1.3; 5.5.3
10.2	Devices shall be designed, manufactured and packaged in such a way as to minimise the risk posed by contaminants and residues to patients, taking account of the intended purpose of the device, and to the persons involved in the transport, storage and use of the devices. Particular attention shall be paid to tissues exposed to those contaminants and residues and to the duration and frequency of exposure.	5.2.6; 5.3.1.3
10.3	Devices shall be designed and manufactured in such a way as to reduce to a level as low as reasonably practicable the risks posed by substances or particles, including wear debris, degradation products and processing residues, that may be released from the device. Special attention shall be given to substances which are carcinogenic, mutagenic or toxic to reproduction ('CMR'), in accordance with Part 3 of Annex VI to Regulation (EC) No 1272/2008 of the European Parliament and of the Council [(1)] , and to substances having endocrine disrupting properties for which there is scientific evidence of probable serious effects to human health and which are identified in accordance with the procedure set out in Article 59 of Regulation (EC) No 1907/2006 of the European Parliament and of the Council[(2)].	4.1.1.4.e; 5.3.1.5
10.4	Devices shall be designed and manufactured in such a way as to reduce as far as possible the risks posed by the unintentional ingress of substances into the device, taking into account the device and the nature of the environment in which it is intended to be used.	5.2.2; 5.2.6; 5.3.1.5
11	**Infection and microbial contamination**	
11.1	Devices and their manufacturing processes shall be designed in such a way as to eliminate or reduce as far as possible the risk of infection to the user or, where applicable, other persons. The design shall:	5.2.2.; 5.2.6; 5.5.3
a)	allow easy and safe handling;	
b)	reduce as far as possible any microbial leakage from the device and/or microbial exposure during use;	
	and, where necessary	
c)	prevent microbial contamination of the device during use and, in the case of specimen receptacles, the risk of contamination of the specimen.	

	Chapter 2: Requirements regarding design and manufacture	EN ISO 15189 / Remarks
11.2	Devices labelled either as sterile or as having a specific microbial state shall be designed, manufactured and packaged to ensure that their sterile condition or microbial state is maintained under the transport and storage conditions specified by the manufacturer until that packaging is opened at the point of use, unless the packaging which maintains their sterile condition or microbial state is damaged.	
11.3	Devices labelled as sterile shall be processed, manufactured, packaged and, sterilised by means of appropriate, validated methods.	
11.4	Devices intended to be sterilised shall be manufactured and packaged in appropriate and controlled conditions and facilities.	
11.5	Packaging systems for non-sterile devices shall maintain the integrity and cleanliness of the product and, where the devices are to be sterilised prior to use, minimise the risk of microbial contamination; the packaging system shall be suitable taking account of the method of sterilisation indicated by the manufacturer.	
11.6	The labelling of the device shall distinguish between identical or similar devices placed on the market in both a sterile and a non-sterile condition additional to the symbol used to indicate that devices are sterile.	If applicable, indicate on the label
12	**Devices incorporating materials of biological origin**	
	Where devices include tissues, cells and substances of animal, human or microbial origin, the selection of sources, the processing, preservation, testing and handling of tissues, cells and substances of such origin and control procedures shall be carried out so as to provide safety for user or other person.	There is some overlap with sections 5.2.3 and 5.2.6. but it is limited. This part will, if applicable, have to be worked out separately by the laboratory.
	In particular, safety with regard to microbial and other transmissible agents shall be addressed by implementation of validated methods of elimination or inactivation in the course of the manufacturing process. This might not apply to certain devices if the activity of the microbial and other transmissible agent are integral to the intended purpose of the device or when such elimination or inactivation process would compromise the performance of the device.	
13	**Construction of devices and interaction with their environment**	
13.1	If the device is intended for use in combination with other devices or equipment, the whole combination, including the connection system, shall be safe and shall not impair the specified performances of the devices. Any restrictions on use applying to such combinations shall be indicated on the label and/or in the instructions for use.	5.5.3
13.2	Devices shall be designed and manufactured in such a way as to remove or reduce as far as possible:	

	Chapter 2: Requirements regarding design and manufacture	EN ISO 15189 / Remarks
a)	the risk of injury, in connection with their physical features, including the volume/pressure ratio, dimensional and where appropriate ergonomic features;	This will be directly or indirectly already be part of the considerations when initiating an analysis. Also consider applicable working conditions legislation. This part could be specifically included in the risk analysis
b)	risks connected with reasonably foreseeable external influences or environmental conditions, such as magnetic fields, external electrical and electromagnetic effects, electrostatic discharge, radiation associated with diagnostic or therapeutic procedures, pressure, humidity, temperature, variations in pressure and acceleration or radio signal interferences;	5.2.2; 5.2.6
c)	the risks associated with the use of the device when it comes into contact with materials, liquids, and substances, including gases, to which it is exposed during normal conditions of use;	5.2.2.c and e; 5.2.6
d)	the risks associated with the possible negative interaction between software and the IT environment within which it operates and interacts;	5.10.3
e)	the risks of accidental ingress of substances into the device;	5.2.2;5.2.6
f)	the risk of incorrect identification of specimens and the risk of erroneous results due to, for example, confusing colour and/or numeric and/or character codings on specimen receptacles, removable parts and/or accessories used with devices in order to perform the test or assay as intended;	5.4.6
g)	the risks of any foreseeable interference with other devices.	5.5.1.2; 5.5.1.3
13.3	Devices shall be designed and manufactured in such a way as to minimise the risks of fire or explosion during normal use and in single fault condition. Particular attention shall be paid to devices the intended use of which includes exposure to or use in association with flammable or explosive substances or substances which could cause combustion.	5.2.6
13.4	Devices shall be designed and manufactured in such a way that adjustment, calibration, and maintenance can be done safely and effectively.	5.5.1.2; 5.5.1.3
13.5	Devices that are intended to be operated together with other devices or products shall be designed and manufactured in such a way that the interoperability and compatibility are reliable and safe.	5.5.1;5.5.3
13.6	Devices shall be designed and manufactured in such a way as to facilitate their safe disposal and the safe disposal of related waste substances by users, or other person. To that end, manufacturers shall identify and test procedures and measures as a result of which their devices can be safely disposed after use. Such procedures shall be described in the instructions for use.	5.2.2; 5.5.3

	Chapter 2: Requirements regarding design and manufacture	EN ISO 15189 / Remarks
13.7	The measuring, monitoring or display scale (including colour change and other visual indicators) shall be designed and manufactured in line with ergonomic principles, taking account of the intended purpose, users and the environmental conditions in which the devices are intended to be used.	5.2.6
14	**Devices with a measuring function**	
14.1	Devices having a primary analytical measuring function shall be designed and manufactured in such a way as to provide appropriate analytical performance in accordance with point (a) of Section 9.1 of Annex I, taking into account the intended purpose of the device.	5.5.3: 5.5.1.3
14.2	The measurements made by devices with a measuring function shall be expressed in legal units conforming to the provisions of Council Directive 80/181/EEC [(3)].	Laboratories deliberately choose particular their units
15	**Protection against radiation**	If applicable, Section 15 must be worked out separately by the laboratory.
15.1	Devices shall be designed, manufactured and packaged in such a way that exposure of users or other persons to radiation (intended, unintended, stray or scattered) is reduced as far as possible and in a manner that is compatible with the intended purpose, whilst not restricting the application of appropriate specified levels for diagnostic purposes.	There is some overlap with paragraphs 5.2.2; 5.2.3 en 5.2.6
15.2	When devices are intended to emit hazardous, or potentially hazardous, ionizing and/or non-ionizing radiation, they shall as far as possible be:	
a)	designed and manufactured in such a way as to ensure that the characteristics and the quantity of radiation emitted can be controlled and/or adjusted; and	
b)	fitted with visual displays and/or audible warnings of such emissions.	
15.3	The operating instructions for devices emitting hazardous or potentially hazardous radiation shall contain detailed information as to the nature of the emitted radiation, the means of protecting the user, and on ways of avoiding misuse and of reducing the risks inherent to installation as far as possible and appropriate. Information regarding the acceptance and performance testing, the acceptance criteria, and the maintenance procedure shall also be specified.	
16	**Electronic programmable systems — devices that incorporate electronic programmable systems and software that are devices in themselves**	

	Chapter 2: Requirements regarding design and manufacture	EN ISO 15189 / Remarks
16.1	Devices that incorporate electronic programmable systems, including software, or software that are devices in themselves, shall be designed to ensure repeatability, reliability and performance in line with their intended use. In the event of a single fault condition, appropriate means shall be adopted to eliminate or reduce as far as possible consequent risks or impairment of performance.	5.5.1
16.2	For devices that incorporate software or for software that are devices in themselves, the software shall be developed and manufactured in accordance with the state of the art taking into account the principles of development life cycle, risk management, including information security, verification and validation.	For Section 16 reference is made to: 1. MDCG 2019-11 Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR 2. IEC-62304 Medical Device software - software life cycle processes 3. NFU guidance document Software
16.3	Software referred to in this Section that is intended to be used in combination with mobile computing platforms shall be designed and manufactured taking into account the specific features of the mobile platform (e.g. size and contrast ratio of the screen) and the external factors related to their use (varying environment as regards level of light or noise).	
16.4	Manufacturers shall set out minimum requirements concerning hardware, IT networks characteristics and IT security measures, including protection against unauthorised access, necessary to run the software as intended.	15.10.3
17	**Devices connected to or equipped with an energy source**	If applicable, Section 17 will have to be worked out separately by the laboratory. This section will seldom apply to in-house LDTs. See 5.2.2.c
17.1	For devices connected to or equipped with an energy source, in the event of a single fault condition, appropriate means shall be adopted to eliminate or reduce as far as possible consequent risks.	
17.2	Devices where the safety of the patient depends on an internal power supply shall be equipped with a means of determining the state of the power supply and an appropriate warning or indication for when the capacity of the power supply becomes critical. If necessary, such warning or indication shall be given prior to the power supply becoming critical.	
17.3	Devices shall be designed and manufactured in such a way as to reduce as far as possible the risks of creating electromagnetic interference which could impair the operation of the device in question or other devices or equipment in the intended environment.	
17.4	Devices shall be designed and manufactured in such a way as to provide a level of intrinsic immunity to electromagnetic interference such that is adequate to enable them to operate as intended.	

	Chapter 2: Requirements regarding design and manufacture	EN ISO 15189 / Remarks
17.5	Devices shall be designed and manufactured in such a way as to avoid as far as possible the risk of accidental electric shocks to the user, or other person both during normal use of the device and in the event of a single fault condition in the device, provided the device is installed and maintained as indicated by the manufacturer.	
18	**Protection against mechanical and thermal risks**	If applicable, Section 18 will have to be worked out separately by the laboratory. This section will seldom apply to in-house LDTs.
18.1	Devices shall be designed and manufactured in such a way as to protect users and other persons against mechanical risks.	
18.2	Devices shall be sufficiently stable under the foreseen operating conditions. They shall be suitable to withstand stresses inherent to the foreseen working environment, and to retain this resistance during the expected lifetime of the devices, subject to any inspection and maintenance requirements as indicated by the manufacturer.	
18.3	Where there are risks due to the presence of moving parts, risks due to break-up or detachment, or leakage of substances, then appropriate protection means shall be incorporated. Any guards or other means included with the device to provide protection, in particular against moving parts, shall be secure and shall not interfere with access for the normal operation of the device, or restrict routine maintenance of the device as intended by the manufacturer.	
18.4	Devices shall be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from vibration generated by the devices, taking account of technical progress and of the means available for limiting vibrations, particularly at source, unless the vibrations are part of the specified performance.	
18.5	Devices shall be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from the noise emitted, taking account of technical progress and of the means available to reduce noise, particularly at source, unless the noise emitted is part of the specified performance.	
18.6	Terminals and connectors to the electricity, gas or hydraulic and pneumatic energy supplies which the user or other person has to handle, shall be designed and constructed in such a way as to minimise all possible risks.	
18.7	Errors likely to be made when fitting or refitting certain parts which could be a source of risk shall be made impossible by the design and construction of such parts or, failing this, by information given on the parts themselves and/or their housings. The same information shall be given on moving parts and/or their housings where the direction of movement needs to be known in order to avoid a risk.	

	Chapter 2: Requirements regarding design and manufacture	EN ISO 15189 / Remarks
18.8	Accessible parts of devices (excluding the parts or areas intended to supply heat or reach given temperatures) and their surroundings shall not attain potentially dangerous temperatures under normal conditions of use.	
19	**Protection against the risks posed by devices intended for self-testing or near-patient testing**	Not applicable, LDTs are in principle not made for self-testing or near-patient testing
19.1	Devices intended for self-testing or near-patient testing shall be designed and manufactured in such a way that they perform appropriately for their intended purpose taking into account the skills and the means available to the intended user and the influence resulting from variation that can be reasonably anticipated in the intended user's technique and environment. The information and instructions provided by the manufacturer shall be easy for the intended user to understand and apply in order to correctly interpret the result provided by the device and to avoid misleading information. In the case of near-patient testing, the information and the instructions provided by the manufacturer shall make clear the level of training, qualifications and/or experience required by the user.	
19.2	Devices intended for self-testing or near-patient testing shall be designed and manufactured in such a way as to:	Not applicable, LDTs are in principle not made for self-testing or near-patient testing
a)	ensure that the device can be used safely and accurately by the intended user at all stages of the procedure if necessary after appropriate training and/or information; and	
b)	reduce as far as possible the risk of error by the intended user in the handling of the device and, if applicable, the specimen, and also in the interpretation of the results.	
19.3	Devices intended for self-testing and near-patient testing shall, where feasible, include a procedure by which the intended user:	
a)	can verify that, at the time of use, the device will perform as intended by the manufacturer; and	
b)	be warned if the device has failed to provide a valid result.	

[(1)] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

[(2)] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

[(3)] Council Directive 80/181/EEC of 20 December 1979 on the approximation of the laws of the Member States relating to units of measurement and on the repeal of Directive 71/354/EEC

Explanation to Chapter 3, section 20

The question is whether and to what extent components 20.1, 20.2 and 20.3 apply to Lab Developed Tests. Tests are made and used within an institute and the "manufacturer" is usually the user.

In general terms, the scope of this section is that: each device must be accompanied by the information necessary to identify the device and its manufacturer, and any safety and performance information relevant to the users or other persons, when relevant. This information may be provided on the device itself or on the packaging, or it may be stated in the instructions for use. In other words, relevant information must be available to the user. For this you have Standard Operating Procedures (SOPs), labels, registrations, instructions for use, etc. This is in line with, for example, EN ISO 15189 items 5.3.2.7 and 5.5.3.

	Chapter 3: Requirements regarding information supplied with the device	EN ISO 15189 / Remarks
20	**Label and instructions for use**	
20.1	**Algemene eisen met betrekking tot de door de fabrikant geleverde informatie** Each device shall be accompanied by the information needed to identify the device and its manufacturer, and by any safety and performance information relevant to the user or any other person, as appropriate. Such information may appear on the device itself, on the packaging or in the instructions for use, and shall, if the manufacturer has a website, be made available and kept up to date on the website, taking into account the following:	Advice for members for Section 20.1: determine for each part whether it applies and whether it complies See Explanation to Chapter 3 . See 5.3
a)	The medium, format, content, legibility, and location of the label and instructions for use shall be appropriate to the particular device, its intended purpose and the technical knowledge, experience, education or training of the intended user(s). In particular, instructions for use shall be written in terms readily understood by the intended user and, where appropriate, supplemented with drawings and diagrams.	
b)	The information required on the label shall be provided on the device itself. If this is not practicable or appropriate, some or all of the information may appear on the packaging for each unit. If individual full labelling of each unit is not practicable, the information shall be set out on the packaging of multiple devices.	
c)	Labels shall be provided in a human-readable format and may be supplemented by machine-readable information, such as radio-frequency identification or bar codes.	

	Chapter 3: Requirements regarding information supplied with the device	EN ISO 15189 / Remarks
d)	Instructions for use shall be provided together with devices. However, in duly justified and exceptional cases instructions for use shall not be required or may be abbreviated if the device can be used safely and as intended by the manufacturer without any such instructions for use.	
e)	Where multiple devices, with the exception of devices intended for self-testing or near-patient testing, are supplied to a single user and/or location, a single copy of the instructions for use may be provided if so agreed by the purchaser who in any case may request further copies to be provided free of charge.	
f)	When the device is intended for professional use only, instructions for use may be provided to the user in non-paper format (e.g. electronic), except when the device is intended for near-patient testing.	
g)	Residual risks which are required to be communicated to the user and/or other person shall be included as limitations, contra-indications, precautions or warnings in the information supplied by the manufacturer.	
h)	Where appropriate, the information supplied by the manufacturer shall take the form of internationally recognised symbols, taking into account the intended users. Any symbol or identification colour used shall conform to the harmonised standards or CS. In areas for which no harmonised standards or CS exist, the symbols and colours shall be described in the documentation supplied with the device.	
i)	In the case of devices containing a substance or a mixture which may be considered as being dangerous, taking account of the nature and quantity of its constituents and the form under which they are present, relevant hazard pictograms and labelling requirements of Regulation (EC) No 1272/2008 shall apply. Where there is insufficient space to put all the information on the device itself or on its label, the relevant hazard pictograms shall be put on the label and the other information required by Regulation (EC) No 1272/2008 shall be given in the instructions for use.	
j)	The provisions of Regulation (EC) No 1907/2006 on the safety data sheet shall apply, unless all relevant information, as appropriate, is already made available in the instructions for use.	
20.2	**Information on the label** The label shall bear all of the following particulars:	Advice for members for Section 20.2: If applicable, include this necessary information on any packaging, in procedures / registrations, etc. See Explanation to Chapter 3.
a)	the name or trade name of the device;	

	Chapter 3: Requirements regarding information supplied with the device	EN ISO 15189 / Remarks
b)	the details strictly necessary for a user to identify the device and, where it is not obvious for the user, the intended purpose of the device;	The strictly necessary data to identify tool, see 5.3.2.7
c)	the name, registered trade name or registered trade mark of the manufacturer and the address of its registered place of business;	Not applicable, LDTs are developed in-house
d)	if the manufacturer has its registered place of business outside the Union, the name of its authorised representative and the address of the registered place of business of the authorised representative;	Not applicable, LDTs are developed in-house
e)	an indication that the device is an in vitro diagnostic medical device, or if the device is a 'device for performance study', an indication of that fact;	Not applicable, LDTs are developed in-house
f)	the lot number or the serial number of the device preceded by the words LOT NUMBER or SERIAL NUMBER or an equivalent symbol, as appropriate;	If applicable; 5.3.2.7
g)	the UDI carrier as referred to in Article 24 and Part C of Annex VI;	Not applicable, necessary if CE marking is present
h)	an unambiguous indication of the time limit for using the device safely, without degradation of performance, expressed at least in terms of year and month and, where relevant, the day, in that order;	Consistent with 5.3.2.7 en 5.5.3
i)	where there is no indication of the date until when it may be used safely, the date of manufacture. This date of manufacture may be included as part of the lot number or serial number, provided the date is clearly identifiable;	Consistent with 5.3.2.7
j)	where relevant, an indication of the net quantity of contents, expressed in terms of weight or volume, numerical count, or any combination of thereof, or other terms which accurately reflect the contents of the package;	If applicable
k)	an indication of any special storage and/or handling condition that applies;	If applicable; 5.3.2.7
l)	where appropriate, an indication of the sterile state of the device and the sterilisation method, or a statement indicating any special microbial state or state of cleanliness;	If applicable
m)	warnings or precautions to be taken that need to be brought to the immediate attention of the user of the device or to any other person. This information may be kept to a minimum in which case more detailed information shall appear in the instructions for use, taking into account the intended users;	5.3.2.7; 5.5.3
n)	if the instructions for use are not provided in paper form in accordance with point (f) of Section 20.1, a reference to their accessibility (or availability), and where applicable the website address where they can be consulted;	Not applicable; user manual is included in SOPS
o)	where applicable, any particular operating instructions;	5.3.2.7; 5.5.3

	Chapter 3: Requirements regarding information supplied with the device	EN ISO 15189 / Remarks
p)	if the device is intended for single use, an indication of that fact. A manufacturer's indication of single use shall be consistent across the Union;	Not applicable, LDT's are not made for self-testing or near-patient testing
q)	if the device is intended for self-testing or near-patient testing, an indication of that fact;	Not applicable, LDT's are not made for self-testing or near-patient testing
r)	where rapid assays are not intended for self-testing or near-patient testing, the explicit exclusion hereof;	Not applicable, LDT's are not made for self-testing or near-patient testing
s)	where device kits include individual reagents and articles that are made available as separate devices, each of those devices shall comply with the labelling requirements contained in this Section and with the requirements of this Regulation;	If applicable; 5.3.2.7
t)	the devices and separate components shall be identified, where applicable in terms of batches, to allow all appropriate action to detect any potential risk posed by the devices and detachable components. As far as practicable and appropriate, the information shall be set out on the device itself and/or, where appropriate, on the sales packaging;	If applicable; 5.3.2.7
u	the label for devices for self-testing shall bear the following particulars: i) the type of specimen(s) required to perform the test (e.g. blood, urine or saliva); ii) the need for additional materials for the test to function properly; iii) contact details for further advice and assistance. The name of devices for self-testing shall not reflect an intended purpose other than that specified by the manufacturer.	Not applicable, LDT's are not made for self-testing or near-patient testing, see Section 9.4
20.3	**Information on the packaging which maintains the sterile condition of a device ('sterile packaging'):** The following particulars shall appear on the sterile packaging:	Advice for members for Section 20.3: If applicable, include this necessary information on any packaging, in procedures / registrations, etc. See Explanation to Chapter 3 See 5.3
a)	an indication permitting the sterile packaging to be recognised as such,	
b)	a declaration that the device is in a sterile condition,	
c)	the method of sterilisation,	
d)	the name and address of the manufacturer,	
e)	een beschrijving van het hulpmiddel;	
f)	a description of the device,	
g)	an unambiguous indication of the time limit for using the device safely, expressed at least in terms of year and month and, where relevant, the day, in that order,	

	Chapter 3: Requirements regarding information supplied with the device	EN ISO 15189 / Remarks
h)	an instruction to check the instructions for use for what to do if the sterile packaging is damaged or unintentionally opened before use.	
20.4	**Information in the instructions for use**	
20.4.1	The instructions for use shall contain all of the following particulars:	
a)	the name or trade name of the device;	5.5.3
b)	the details strictly necessary for the user to uniquely identify the device;	5.5.3
c)	the device's intended purpose: i) what is detected and/or measured; ii) its function (e.g. screening, monitoring, diagnosis or aid to diagnosis, prognosis, prediction, companion diagnostic); iii) the specific information that is intended to be provided in the context of: - a physiological or pathological state; - congenital physical or mental impairments; - the predisposition to a medical condition or a disease; - the determination of the safety and compatibility with potential recipients; - the prediction of treatment response or reactions; - the definition or monitoring of therapeutic measures; iv) whether it is automated or not; v) whether it is qualitative, semi-quantitative or quantitative; vi) the type of specimen(s) required; vii) where applicable, the testing population; and	5.5.3
	viii) for companion diagnostics, the International Non-proprietary Name (INN) of the associated medicinal product for which it is a companion test.	If applicable, this should be worked out
d)	an indication that the device is an in vitro diagnostic medical device, or, if the device is a 'device for performance study', an indication of that fact;	This will be implicitly complied to a work instruction / SOP / instructions for use. See 5.5.3
e)	the intended user, as appropriate (e.g. self-testing, near patient and laboratory professional use, healthcare professionals);	5.5.3
f)	the test principle;	5.5.3
g)	a description of the calibrators and controls and any limitation upon their use (e.g. suitable for a dedicated instrument only);	5.5.3

	Chapter 3: Requirements regarding information supplied with the device	EN ISO 15189 / Remarks
h)	a description of the reagents and any limitation upon their use (e.g. suitable for a dedicated instrument only) and the composition of the reagent product by nature and amount or concentration of the active ingredient(s) of the reagent(s) or kit as well as a statement, where appropriate, that the device contains other ingredients which might influence the measurement;	5.5.3
i)	a list of materials provided and a list of special materials required but not provided;	5.5.3
j)	for devices intended for use in combination with or installed with or connected to other devices and/or general purpose equipment: - information to identify such devices or equipment, in order to obtain a validated and safe combination, including key performance characteristics, and/or - information on any known restrictions to combinations of devices and equipment.	5.5.3
k)	an indication of any special storage (e.g. temperature, light, humidity, etc.) and/or handling conditions which apply;	5.2.6; 5.5.3
l)	in-use stability which may include the storage conditions, and shelf life following the first opening of the primary container, together with the storage conditions and stability of working solutions, where this is relevant;	5.3.2.7; 5.5.3
m)	if the device is supplied as sterile, an indication of its sterile state, the sterilisation method and instructions in the event of the sterile packaging being damaged before use;	If applicable, this should be worked out. 5.3.1.2
n)	information that allows the user to be informed of any warnings, precautions, measures to be taken and limitations of use regarding the device. That information shall cover, where appropriate: i) warnings, precautions and/or measures to be taken in the event of malfunction of the device or its degradation as suggested by changes in its appearance that may affect performance, ii) warnings, precautions and/or measures to be taken as regards the exposure to reasonably foreseeable external influences or environmental conditions, such as magnetic fields, external electrical and electromagnetic effects, electrostatic discharge, radiation associated with diagnostic or therapeutic procedures, pressure, humidity, or temperature, iii) warnings, precautions and/or measures to be taken as regards the risks of interference posed by the reasonably foreseeable presence of the device during specific diagnostic investigations, evaluations, therapeutic treatment or other procedures such as electromagnetic interference emitted by the device affecting other equipment, iv) precautions related to materials incorporated into the device that contain or consist of CMR substances, or endocrine disrupting substances or that could result in sensitisation or an allergic reaction by the patient or user,	5.2.6; 5.5.3

	Chapter 3: Requirements regarding information supplied with the device	EN ISO 15189 / Remarks
	v) if the device is intended for single use, an indication of that fact. A manufacturer's indication of single use shall be consistent across the Union, vi) if the device is reusable, information on the appropriate processes to allow reuse, including cleaning, disinfection, decontamination, packaging and, where appropriate, the validated method of re-sterilisation. Information shall be provided to identify when the device should no longer be reused, such as signs of material degradation or the maximum number of allowable reuses;	5.2.6; 5.5.3
o)	any warnings and/or precautions related to potentially infectious material that is included in the device;	5.5.3
p)	where relevant, requirements for special facilities, such as a clean room environment, or special training, such as on radiation safety, or particular qualifications of the intended user;	5.5.3
q)	conditions for collection, handling, and preparation of the specimen;	5.4.4.1; 5.5.3
r)	details of any preparatory treatment or handling of the device before it is ready for use, such as sterilisation, final assembly, calibration, etc., for the device to be used as intended by the manufacturer;	5.5.3
s)	the information needed to verify whether the device is properly installed and is ready to perform safely and as intended by the manufacturer, together with, where relevant: i) details of the nature, and frequency, of preventive and regular maintenance, including cleaning and disinfection; ii) identification of any consumable components and how to replace them; iii) information on any necessary calibration to ensure that the device operates properly and safely during its intended lifetime; iv) methods for mitigating the risks encountered by persons involved in installing, calibrating or servicing devices.	5.3.1.3 up to 5.3.1.7; 5.5.3
t)	where applicable, recommendations for quality control procedures;	5.5.3.k
u)	the metrological traceability of values assigned to calibrators and control materials, including identification of applied reference materials and/or reference measurement procedures of higher order and information regarding maximum (self-allowed) batch to batch variation provided with relevant figures and units of measure;	5.3.1.4; 5.5.3
v)	assay procedure including calculations and interpretation of results and where relevant if any confirmatory testing shall be considered; where applicable, the instructions for use shall be accompanied by information regarding batch to batch variation provided with relevant figures and units of measure;	5.5.3.m up to p

	Chapter 3: Requirements regarding information supplied with the device	EN ISO 15189 / Remarks
w)	analytical performance characteristics, such as analytical sensitivity, analytical specificity, trueness (bias), precision (repeatability and reproducibility), accuracy (resulting from trueness and precision), limits of detection and measurement range, (information needed for the control of known relevant interferences, cross-reactions and limitations of the method), measuring range, linearity and information about the use of available reference measurement procedures and materials by the user;	5.5.1.2; 5.5.1.3; 5.5.3.c
x)	clinical performance characteristics as defined in Section 9.1 of this Annex;	5.5.1.2; 5.5.1.3; 5.5.3
y)	the mathematical approach upon which the calculation of the analytical result is made;	5.5.3.m
z)	where relevant, clinical performance characteristics, such as threshold value, diagnostic sensitivity and diagnostic specificity, positive and negative predictive value;	5.5.3.m up to p
aa)	where relevant, reference intervals in normal and affected populations;	5.5.2; 5.5.3 m up to p
ab)	information on interfering substances or limitations (e.g. visual evidence of hyperlipidaemia or haemolysis, age of specimen) that may affect the performance of the device;	5.5.3
ac)	warnings or precautions to be taken in order to facilitate the safe disposal of the device, its accessories, and the consumables used with it, if any. This information shall cover, where appropriate: i) infection or microbial hazards, such as consumables contaminated with potentially infectious substances of human origin; ii) environmental hazards such as batteries or materials that emit potentially hazardous levels of radiation); iii) physical hazards such as explosion.	5.5.3
ad)	the name, registered trade name or registered trade mark of the manufacturer and the address of its registered place of business at which he can be contacted and its location be established, together with a telephone number and/or fax number and/or website address to obtain technical assistance;	Not applicable., LDTs are developed in-house and may not be transferred
ae)	date of issue of the instructions for use or, if they have been revised, date of issue and identifier of the latest revision of the instructions for use, with a clear indication of the introduced modifications;	4.3; 5.5.3
af)	a notice to the user that any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established;	4.9 Reports and incidents are made, this is also a requirement within EN ISO 15189. In addition, this will be posted within a hospital via incident reports, incident committees, etc. In the event of a calamity a report will be sent to the inspection.

	Chapter 3: Requirements regarding information supplied with the device	EN ISO 15189 / Remarks
ag)	where device kits include individual reagents and articles that may be made available as separate devices, each of these devices shall comply with the instructions for use requirements contained in this Section and with the requirements of this Regulation;	If applicable, this should be worked out
ah)	for devices that incorporate electronic programmable systems, including software, or software that are devices in themselves, minimum requirements concerning hardware, IT networks characteristics and IT security measures, including protection against unauthorised access, necessary to run the software as intended.	5.10.3
20.4.2	In addition, the instructions for use for devices intended for self-testing shall comply with all of the following principles:	Not applicable, LDT's are not made for self-testing or near-patient testing
a)	details of the test procedure shall be given, including any reagent preparation, specimen collection and/or preparation and information on how to run the test and interpret the results;	
b)	specific particulars may be omitted provided that the other information supplied by the manufacturer is sufficient to enable the user to use the device and to understand the result(s) produced by the device;	
c)	the device's intended purpose shall provide sufficient information to enable the user to understand the medical context and to allow the intended user to make a correct interpretation of the results;	
d)	the results shall be expressed and presented in a way that is readily understood by the intended user;	
e)	information shall be provided with advice to the user on action to be taken (in case of positive, negative or indeterminate result), on the test limitations and on the possibility of false positive or false negative result. Information shall also be provided as to any factors that can affect the test result such as age, gender, menstruation, infection, exercise, fasting, diet or medication;	
f)	the information provided shall include a statement clearly directing that the user should not take any decision of medical relevance without first consulting the appropriate healthcare professional, information on disease effects and prevalence, and, where available, information specific to the Member State(s) where the device is placed on the market on where a user can obtain further advice such as national helplines, websites;	
g)	for devices intended for self-testing used for the monitoring of a previously diagnosed existing disease or condition, the information shall specify that the patient should only adapt the treatment if he has received the appropriate training to do so.	

5.2 Appendix B Declaration lab-developed tests

Part A Information about the manufacturing health institution	
Institute / Laboratory	
Name:	
Department:	
Address:	
Contact person	
Name:	
Job Title:	
Telephone number:	
E-mail:	
Declaration	
Above mentioned institution states for all tests listed in part B: i) This test is manufactured or modified by this health institution under EN ISO15189 accreditation. ii) This test is compliant with relevant general safety and performance rules as depicted in Annex I of IVDR 2017/746. iii) Deviations from Annex I of IVDR 2017/746 are substantiated and documented in the quality management system. iv) Argumentation for use of lab-developed tests is documented in the quality management system.	
Signed on behalf of the organization	
Name:	
Date:	
Signature:	

Part B Description Lab-developed tests*		Identification
1		
2		

** If desired, the table can indicate which type of LDT is involved (eg developed in-house, research use only test or IVD test with modifications).*