ISO-15189 audit of IVDR compliant LDTs

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IVDR: What are In-House Lab Developed Tests?

- IVDR Art 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 the conditions of art 5 are met**

Conclusion:
art 5 and relevant parts of ANNEX I apply
other requirements of the IVDR shall not be invoked
(MDCG guidance is not legally binding)

IVDR: art 5 summarized / paraphrased

EU 2017/746 IVDR 5(5)

- (a) not transferred to an other legal entity (HI) = **IN-HOUSE**
- (b) manufacture and use occur under appropriate quality management systems
- (c) compliance with standard EN ISO 15189
  or where applicable national provisions, including provisions regarding accreditation
- (d) documentary justification that target patient needs are
  not met at appropriate level of performance by an equivalent device available on the market
- (e) provide documentation to CA upon request on used LDTs, with justification of manufacturing, modifications and use
- (f) publicly available declaration of name, address manufacturing entity, identifying details of the devices,
  and a general confirmation of adherence to Annex I of the IVDR, or justification of not-fully met requirements
- (g) for high-risk **class D devices** by the rules of annex VIII documentation for the benefit of the CA,
  with sufficient detail to understand the **manufacturing facility** and **manufacturing process**,
  and **design** and p**erformance data** and **intended use**
  to enable the CA to ascertain that requirements of Annex I are fulfilled.
  The national legislator can extend this to lower risk classes.
- (h) HI assures that it does what it says in the above documentation
- (i) HI reviews **experience gained from clinical use**, and takes **necessary corrective actions**

IVDR refers to ISO-15189 in art. 5(5)c

- IVDR:
  the laboratory of the health institution is compliant with standard EN ISO 15189 or where applicable national provisions, including national provisions regarding accreditation

- ISO 15189: 1 Scope

  2012: can be used for confirming or recognizing the competence of medical laboratories by …, regulatory authorities, …
  Note: International, national or regional regulations or requirements may also apply to specific topics covered in this International Standard.

  2022: applicable for confirming or recognizing the competence of medical laboratories by …, regulatory authorities, …
  Note: International, national, or regional regulations or requirements can also apply to specific topics covered in this document.

- CONCLUSION
  - ISO requires adherence to the law
  - Hierarchical systems: allow for “national” implementations
  - Different national / regional authorities can work together

EU IVDR Requirement for ISO 15189 – equivalent QS

EU 2017/746 IVDR 5(5)

- Refers to ISO 15189 (5.5 c)
- Allowed Lab Developed Tests (5.5 d)
- Intended purpose (5.5 d)
- Scientific validity (Annex I)
- Clinical performance (Annex I 9.1 a)
- Analytical performance (Annex I 9.1 b)
- Safety (5.5 f iii, Annex I Chp I)
- Surveillance (5.5 I, Annex I 9.2)
- Manufacturing of devices (5.5 g, h)
- Draw-up statements for authorities (5.5 e, f)
- Transparency to users (5.5 f)

ISO 15189:2012

- Primacy of legally-binding regulations (Introduction, 1)
- Conditions requiring “validation” (5.5.1.3 a-d)
- Fit-for intended use (5.5.1.3)
- Preferred procedures (5.5.1.1)
- Requirements for intended use fulfilled (5.5.1.3)
- Analytical Performance (5.5.1.3)
- Risk management (4.14.6) & Safety (5.2.1)
- Management Review (4.15.2 a)
- Equipment (5.3.1), Reagents and consumables (5.3.2)
- Register validation-file (5.5.1.2)
- Information for users (5.4.2)

- Requirements of the **IVDR map well on the ISO 15189** framework : **It is a sufficient standard**
- IVDR 5(5) c
  - implicitely elevates ISO15189 to the level of a harmonized standard
  - ISO 15189 leaves space for national provisions on licensing and accreditation

LDT improves Benefit/Risk Ratio

- LDT (new design or modified commercial device) justified when
  - “no marketed alternative available”
  - “marketed variants are unfit” for HI intended use

Justification has to be documented

Justification = improved Benefit/Risk ratio

Common scenario’s that fulfill this condition without problems

- Intended Clinical Use extended = ↑ benefit at ≈ risk
- Redesigned to Improve Performance = ↑ benefit at ↓ risk
- Redesigned to Improve Technical Reliability = ≈ /↑ benefit at ↓ risk

Do IVDR and ISO 15189 have a different take on issues?

- IVDR:
  - Focus is putting in use of physical and software devices
  - Assure that manufactured devices are suited for clinically effective and safe use
- ISO 15189:
  - Focus is diagnostic service
  - Assure that laboratory processes are suited for delivery of effective and safe diagnostic services
  - Manufacturing the LDTs is one step in that process

- Clinical Validity:
  - In the end both systems refer to clinical use as the touch stone

Elements to look for in Validation File of LDT (1/2)

- Starting Point: Intended Use
  - Diagnostic purpose in
  - Patient group
  - By means of Method on Equipment
  - Performed by Laboratory Personnel / Hospital staff / …
- Market exploration:
  - Scientifically valid (alternatives)
  - Measurand: what in which sample, measured by which property (make property element of your performance qualifications)
  - Intended Use defines Performance qualifications: analytical, clinical & organizational
- Justification for in-House test & Risk Classification according to Annex VIII

Elements to look for in Validation File of LDT (2/2)

- Validation based on Risk Management:
  - Performance Qualifications and Risk Management define Validation Plan
  - Manufacturing Process: Facilities and Equipment, Supply Chains, Acceptance Testing,
  - For the patient:
    - Focus on Clinical Validity and Performance
    - Analytical and Clinical performance separately identified in the IVDR
      Often evaluated from the same data in one go
    - Organizational Aspects (e.g longitudinal and trans-mural care)
  - For HI personnel & bystanders
    - Hazardous materials and processes
- Continuous Evaluation:
  - Internal Quality Assurance; External Proficiency Testing (or alternatives)
  - Follow-up of Clinical Experiences
  - CAPA & Management Review

CONCLUSION : IVDR and ISO differ in nothing?
NOTE : Besides the continuous validation of methods/devices other elements of art 5(5) also need auditing

Don’t let Regulation become the Enemy of Quality

- **ISO 15189 is a sufficient instrument to guarantee high-quality manufacture of laboratory developed tests for in-house-use conform requirements of the European In-Vitro-Diagnostics Regulation. Joint opinion of EFLM TF-ERA and WG-A/ISO**
- *Vanstapel F.J.L.A, Orth M, Streichert T., Capoluongo E.D, Oosterhuis W.P, Can Çubukçu H, Bernabeu-Andreu F.A, Thelen M, Jacobs L.H.J, Linko S, Pal Bhattoa H, Bossuyt P.M.M, Meško Brguljan P, Boursier G, Cobbaert C.M and Neumaier M*
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A call for all parties to take up responsibility:
Try to remedy legal uncertainty with more regulation,
and you end up
loosing the freedom to choose for the best solutions
in a complex environment