Validation of Lab Developed Tests
Conform EU IVDR 2017/746 & EN ISO 15189:2012

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(disclaimer: inspired by the situation as of Nov 4, 2021, pending further guidance and implementing acts)

Guiding principles on LDT's: IVDR & ISO 15189

EU 2017/746 IVDR 5(5)

- Clinical Performance
- Patient Safety
- Legal requirement

ISO 15189:2012

- Competence
- Reliable Results
- In principle voluntary

Notes

1. Requirements for the Management System (with respect to LDT's):
Both systems impose in essence identical requirements on the management systems to achieve their goals.
Both imply "systems thinking".

2. Diagnostic Industry:
Manufacturers diagnostic devices used in clinical laboratories / point-of-care testing and over-the-counter self-testing

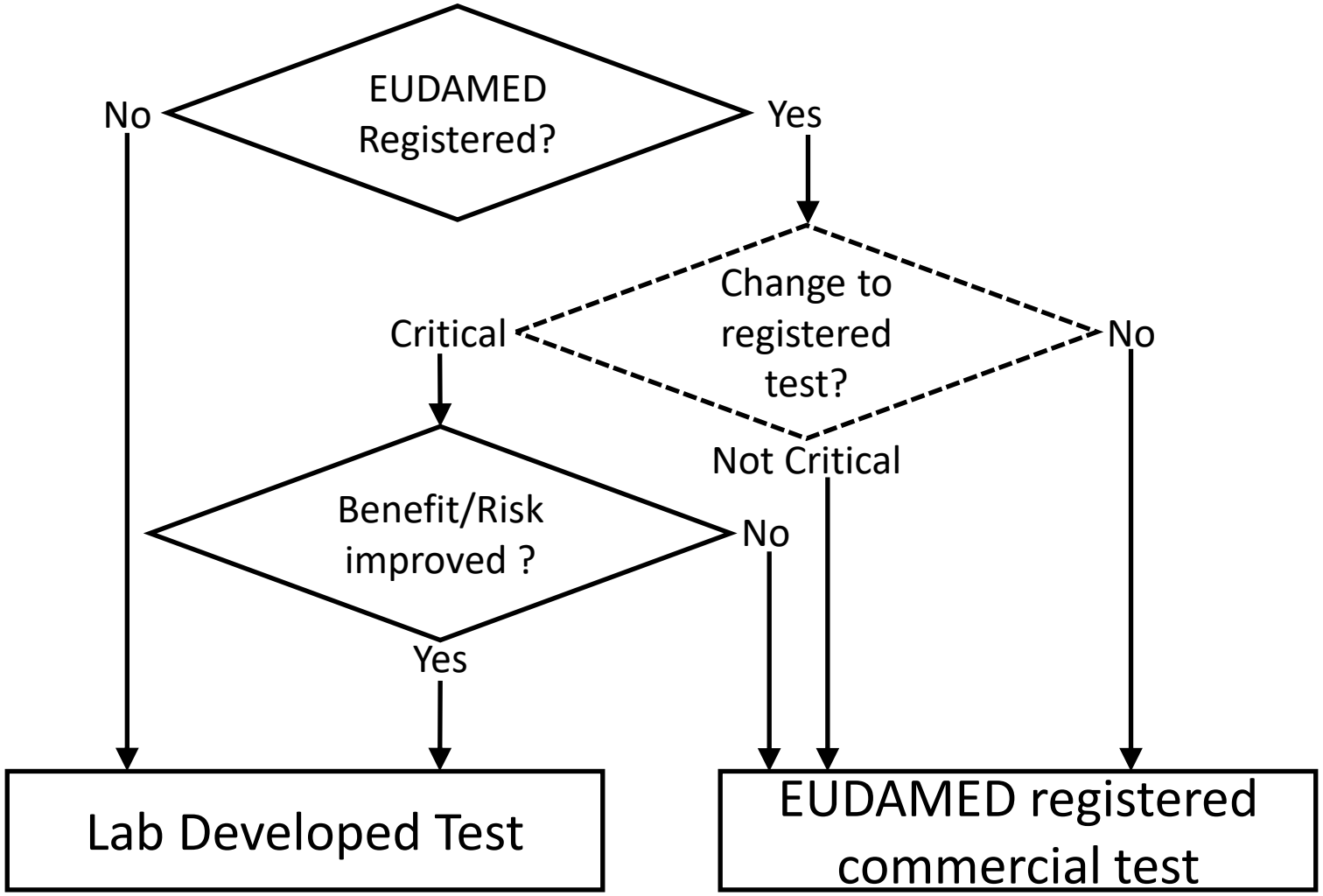
3. Laboratory Medicine:
Provides a diagnostic service by analyzing samples to produce results and by competent consultative services
Participates in the Brain-to-Brain cycle by entering in a deliberation dialogue with users
LDT's are diagnostic procedures in-house designed and applied in the context of intramural / transmural care programs

IVDR Risk-based device classification rules

- ANNEX VIII
  - Rule 1: transmissible disease in blood derived products
    transmissible life threatening agents **class D**
  - Rule 2: immunological compatibility of blood products **class D**
  - Rule 3: mostly all other tests, inclusive POCT class C
  - Rule 4: self-testing class C
    but: pregnancy, fertility, cholesterol class B
    Glc, erythrocytes, leucocytes, bacteria in urine class B
  - Rule 5: general accessories and consumables class A
  - Rule 6: unclassified by the above class B
  - Rule 7: untitrated controls class A

- Class D : draw up documentation to be audited by the national Competent Authority (EU IVDR 5.5 g)
- Class C, B, A : Member State may apply the same provision as for class D

IVDR Risk-based Authorization for Lab Developed Test



Risk-based Validation of LDT's: Significant Changes?

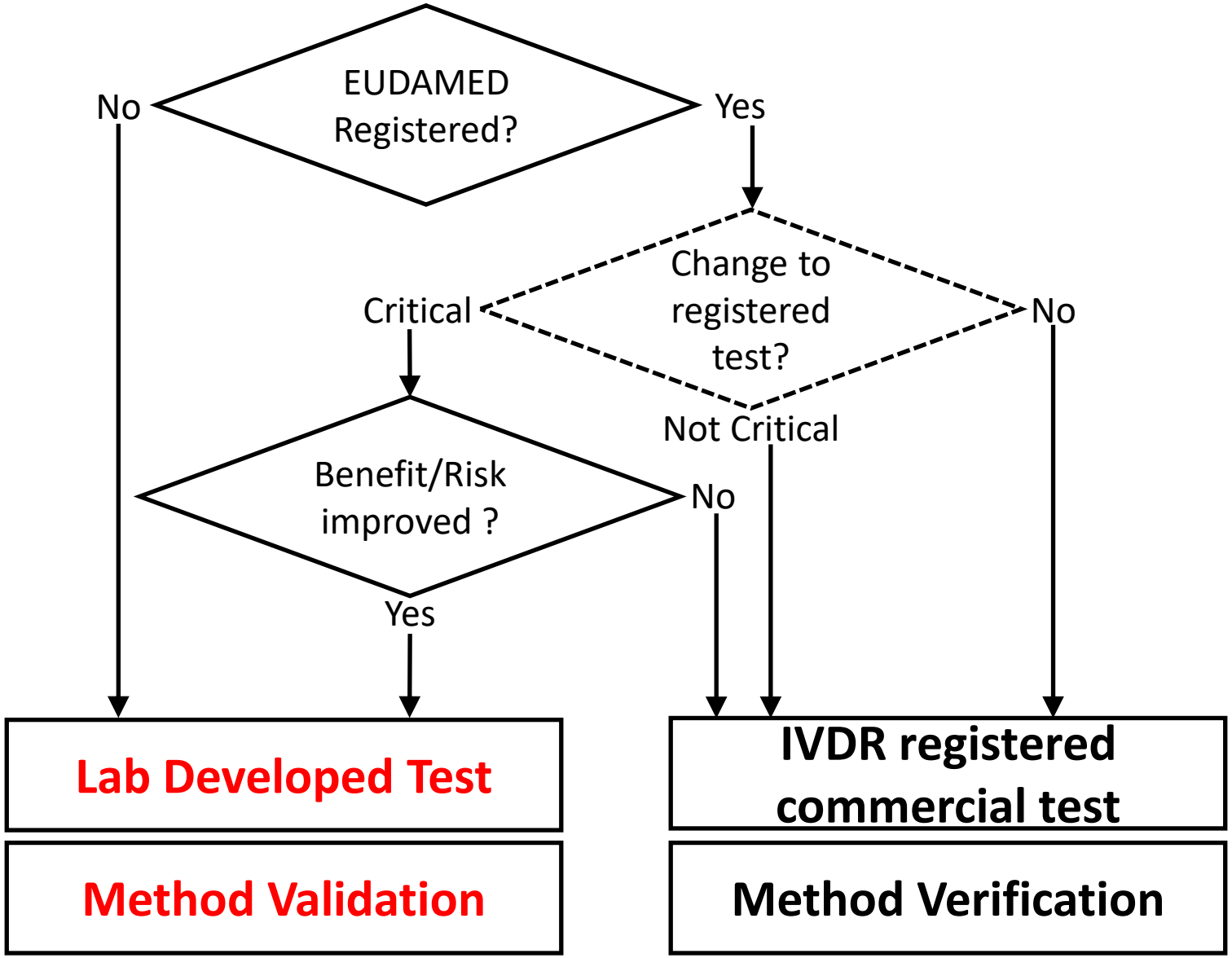
Resources: MDCG 2020-3

Transitional derogations for MDR Art 120.3 as a *model for possible future* IVDR Art 110.3 guidance:
no derogation for EC IVDD labelled products when "significant changes in design and intended purpose" ?

- A. Extension or Change to the Intended Purpose
  - New user or patient population
  - Change of clinical use (anatomical site / sample matrix)
- B. Change in Design or Performance Specification
  - Requires further clinical or usability data
  - New risks / existing risks require Redesign of Control Measures
  - Change to Operating Principles / Control Mechanisms
- C. Change in Software / Interpretation of Results
  - Operating system / database structure / channels of interoperability
  - User interface
  - Algorithms / Diagnostic Features
- D. Change in Materials
  - Change of equipment components / reagents / calibrators
  - Ingredient or material from new supplier does not meet existing specification
  - Change in Shelf Life

Strict guidance impractical for LDT's in a continuum of intended purposes within a continuum of applications and methods?
Guidance documents should be open-ended, identifying listings as non-exhaustive and listed items as dependent on relevance

Risk-based Validation of Lab Developed Test



Method Verification - Method Validation

ISO 15189:2012 5.5.1.2 ISO 15189:2012 5.5.1.3

Define Intended Use / Target Population

Market Exploration Document Scientific Validity

Define Needed Level of Performance

Verify
Level of Performance Achieved

Validate
Analytical Performance
Clinical Performance
Safety

Document Operating Procedure

collect all data
needed to start-up your iQC Program

Resources: Validation and verification of examination procedures in medical laboratories: opinion of the EFLM Working Group Accreditation and ISO/CEN standards (WG-A/ISO) on dealing with ISO 15189:2012 demands for method verification and validation

IVDR MDCG Proposal for Deferred Timeline for LDT's

14.10.2021 2021/0323 (COD)

https://ec.europa.eu/health/sites/default/files/md_newregulations/docs/md_2017-746-regulation_2021-amendment_en.pdf

New Tests & Changes to Existing Tests

May 26 2022 adherence to Annex I remains

Legacy Tests already in Use

in Article 113(3), the following points (i) and (j) are added:
(i) Article 5(5), points (b), (c) and (e) to (i), *(= validation file of devices in use)*
shall apply from 26 May 2024
(j) Article 5(5), point (d), *(= no equivalent device on the market)*
shall apply from 26 May 2028

Don't kick the can down the road!
Get ready: Map existing ISO-15189 compliant validation files to the concordant IVDR requirements

Validation of Lab Developed Tests: map ISO 15189 to EU IVDR

ISO 15189:2012

- Primacy of local 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)

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)

Conclusion: ISO 15189 covers all requirements of the IVDR (is a sufficient standard)

Resources: Handvat gebruik Lab-Developed Tests zoals beschreven in VERORDENING (EU) 2017/746 van 5 april 2017 betreffende medische hulpmiddelen voor in-vitrodiagnostiek

LDT Method Validation

- Intended Purpose - Scientific Validity
- Technical and Analytical Performance
- Clinical Performance
- Conclusion translates into
  - SOP's – Risk Management / Safety Plan / Quality Assurance Plan
- Documentation
  - Authorized & protected against tampering
  - Safety and Performance Summary (SPS) publicly available

LDT Method Validation

1. Intended Purpose = Conception of your LDT = Key Driver of the Validation

- Follow Critically Appraised Topic (CAT) Methodology
  Resources: Evidence-based laboratory medicine – a guide for critical evaluation of in vitro laboratory testing
- CAT prescription - Research Question:
  - Clinical Question / Clinical Scenario
    - screening, monitoring, diagnosis or aid to diagnosis, prognosis, prediction, companion diagnostic, …
    - physiological or pathological state, congenital physical or mental impairments, predisposition to a medical condition or a disease, safety and compatibility with potential transplant recipients, prediction of treatment response or reactions, selecting and monitoring therapeutic measures (companion tests refer to International Non-proprietary Name of Therapeutic), …
  - Measurand(s)
    - in matrix(ces)
    - analytical method (automated or not)
    - measurement type (nominal, ordinal, interval, ratio)
  - Target Population / Prevalence
  - Appropriate Level of Performance
- Market (EUDAMED) Exploration / Literature Search with Evaluation of Level of Evidence
  - Identify “non-equivalences (EU IVDR 5.5 d)”
    = Commercial device doesn’t match needs of target group at appropriate level of performance
- Summarize Safety Issues
  - When you opt for modifying a commercial test: identify the critical changes
- Estimate Benefit/Cost
  - When you opt for modifying a commercial test: the modification should improve the benefit/risk ratio

LDT Method Validation
2a. Life-cycle approach

- Manage Validation as a Dynamic Systems Change (Engineering) Project
  - Keep track of the experiments that build / give rise to your final solution
  - Life-cycle concept: post-start-up surveillance of performance and safety resulting in appropriate actions
- Know where you have to land: Report / SOP's conform IVDR regulations
- Summarize why you opt for LDT
  - Summarize the total process, with special attention for home-assembled components and home-made consumables
  - Document technical and clinical performance
  - Have Standard Operating Procedures covering all elements of the process
  - Have a Quality Assurance Plan that is implemented as written
    - to assure that appropriate performance levels are guaranteed
    - to prevent failures (prim. prevention) or to detect and act on failures (secondary prevention) before they may cause harm (in first instance to the patient)
    - to mitigate harm
  - Throughout the life-cycle of the device document performance and safety issues
  - Have a system to evaluate criticality of changes to the system and validate accordingly
    - Cfr. risk-analysis you made to define the appropriate experiments at the original implementation

LDT Method Validation
2b. Technical Performance

- Evaluate / optimize technical performance of equipment
  - E.g. repeated tuning the experiment to know/optimize technical characteristics such as
    - Signal shapes and intensities
    - Resolution and Linearity
    - Signal offsets (= measurement bias)
    - Random spread on results (= measurement uncertainty)
  - In the end this will translate into
    - Standard Operating Procedures
    - Planned maintenance activities
    - Release / start-up criteria
    - …

LDT Method Validation
2c. Measurand – Traceability of results

- Define the measurand
  - Measured property
  - Technique used
  - Primary sample type, secondary sample, measurement matrix
  - Measurement type: nominal, ordinal, interval or ratio
- Identify the traceability of calibrators
  (and when applicable of control materials with assigned values)
  - Preferably trace to *in-matrix certified reference materials*
  - Preferably use short traceability chains

LDT Method Validation
2d. Identify Critical Elements (Fishbone and Failure-Mode-Effects Analysis)

- Cover complete process:
  - B2B: Advice on which test to choose/Test-Request/Results/Reporting/Advice on interpretation & further actions = from Pre-pre and Pre-analytical over Analytical to Post- and Post-post analytical
  - Analytical process:
    from set-up equipment, preparation/conditioning of consumables,
    sample preparation, running the experiments to output of results
- Risk management:
  - Distinguish between Risk, Failure, Harm
  - Distinguish between avoidable and unavoidable failure, acceptable and unacceptable harm
  - Inventory of signals to identify failure (timely = preferably before any harm is done)
  - Prefer primary prevention (no failure will occur) over secondary prevention (action triggered by failure)
  - Plan mitigation of harm
- Cover critical elements in validation / quality assurance / safety plan
  (for the others argue why they do not need to be covered)
  - Manufacturing aspects for in-house use:
    What do you know about degradation pathways, and appropriate detection of degradation / failure?
    Is the stability of equipment and consumables timely covered by quality control procedures?

LDT Method Validation
2e. Analytical Performance Nominal/Ordinal Qualities

- The measurement type defines the statistical approaches that are available
- **nominal, ordinal** (qualitative, pseudo-quantitative):
  - If an underlying “quantitative” measurement is available consider testing at that level (next slide)
  - Other way (when available, in order of preference)
    - Concordance with golden-standard assignment of the characteristic
    - Chi-square / Kappa tests between equivalent methods
    - The above will test **“clinical performance”** in one go
  - Test repeatedly the same samples (by different operators if relevant)
    - Referring to underlying “quantitative cut-offs”
    - This will provide an estimate on “consistency = uncertainty”
    - This will translate into a quality assurance plan & criteria for evaluating “operator competence”

LDT Method Validation
2f. Analytical Performance Interval/Ratio Quantities

- The measurement type defines the statistical approaches that are available
- **interval, ratio** (quantitative):
  - Quantitative measurements on a continuous scale, without or with zero-point known
  - Test measurement range and linearity
  - Test repeatability at relevant cut-offs
    - This will test **“clinical performance”**
    - Test effect of calibrator lots and calibrations within lot
    - When feasible test “justness” with “certified reference materials in matrix”
    - The above will translate into a “quality assurance plan”
  - Well designed method comparison protocol can realize many of the above in 1 go
    - However method comparison is not always feasible / hence not obligatory

LDT Method Validation
3. Clinical Performance

- This starts with your definition of intended purpose – scientific validity
- When appropriate, evaluate
  - reference intervals, cut-off values in target population
  - analytical validation with respect to accuracy of diagnosis
    - Conformance results with golden standard assignment
    - Conformance results between methods
    - Repeatability around cut-off values
  - effect of performing test on a desired or surrogate outcome measure
  - safety with special focus on the patient

Resources:

Unmet clinical needs – the EFLM checklist Course: Unmet clinical needs (eflm.eu)

From biomarkers to medical tests: The changing landscape of test evaluation Clin Chim Acta (2014) 427:49-57

Biomarker development targeting unmet clinical needs Clin Chim Acta (2016) 460:211-219

LDT Method Validation

4. Standard Operating Procedures = Birth of your LDT

- In generic validation procedure refer to SOP as the conclusion of the validation
- SOP and parametrization of supporting procedures (iQC, lab manual) covers
  - Best way to do LDT
  - Quality assurance plan
    - plan to train users
    - evaluation of competence of users
    - settings used in your (generic) quality control procedures
  - Safety instructions
    - Patient: information, preparation and sampling
    - Personnel (can also be patients) using the device(s)
    - Bystanders / Environment
    - B2B: How you help physicians and patients to understand correctly intended purpose & the results

LDT Method Validation

5. Summary for Patients / Users / Competent Authorities

- The IVDR quality model requires significant changes to be notified to the CA (at least for class D)
- Summary states
  - 5.5.a 5.5.f.i Name and address of health institution / legal entity
  - 5.5.b-c ISO-15189 accreditation status, with reference to the device in question
  - 5.5.d. Justification for LDT : specific patient needs cannot be met otherwise
  - 5.5.g. Classification of device according annex VIII
    - Class D -> communicate with national competent authority
  - Transparency – Publicly available summary statement (e.g. the lab manual for patients and users)
    - 5.5.f.i name address health institution
    - 5.5.f.ii identification of device
    - 5.5.f.iii statement that general safety and performance requirements of Annex I are met
- Document properly functioning QS
  - 5.5.h. measures for continued compliance (e.g. audits)
  - 5.5.i. continuous surveillance and corrective actions where needed