Validation Guidance

for medical laboratories

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Introduction

This document provides validation guidance for medical laboratories, with a particular focus on ensuring that *in vitro* diagnostic devices (IVDs) are fit for their intended purpose in the context of ISO 15189 accreditation requirements. Laboratories have a critical responsibility to verify and, where necessary, validate the performance of IVDs to confirm that manufacturers' claims are accurate and applicable to their own patient population, workflows and the intended clinical use, including whether to be used for diagnosis, screening, monitoring or other purposes. This includes the design and execution of validation and verification studies to assess key performance characteristics such as accuracy, precision, sensitivity, specificity, and reportable range.

In practice, laboratories encounter situations where an IVD is used outside of the conditions described in the manufacturer's instructions for use (IFU), including modifications to sample types, workflows, or analytical parameters. Such "off-label" use, which may be clinically justified, requires robust, documented validation to ensure that patient results remain reliable, safe, and clinically defensible. In addition to validation, laboratories must also comply with regulations and MHRA guidance for off-label use of medical devices.

Off-label use requires that:

- a formal risk assessment is carried out and documented
- the ethical and legal implications are considered
- precautions are implemented to minimise the risk
- the risk assessment is reviewed at suitable intervals
- MHRA approval is obtained for exceptional use of non-complying devices (if necessary)

This obligation applies irrespective of whether the IVD has been validated locally. The same principles apply when an IVD is deployed for a purpose not explicitly intended by the manufacturer, or when it is integrated into laboratory-developed testing processes in a modified form.

While this guidance is focused on IVDs, the principles it outlines, critical assessment of performance claims, rigorous validation under actual conditions of use, and careful documentation, are equally applicable to emerging diagnostic technologies. This includes artificial intelligence laboratory–based diagnostic tools and other novel platforms, which may not yet be explicitly referenced in current regulatory or accreditation frameworks but will increasingly form part of the medical laboratory environment. Adopting these validation principles now will help laboratories remain aligned with the ISO 15189 overarching commitment to quality, competence, and patient safety, regardless of how technologies evolve.

Scope

This guidance applies to medical laboratories conducting validation or verification of *in vitro* diagnostic devices (IVDs) and related laboratory diagnostic systems in accordance with ISO 15189 requirements. It covers:

- **Verification of manufacturers' performance claims** – confirming that analytical and clinical performance specifications provided in the instructions for use (IFU) are met under the laboratory's specific environmental, operational, and patient population conditions.
- **Validation of modified or "off-label" use** – assessing performance where an IVD is used outside of its approved or intended purpose, including changes to sample type, workflow, instrumentation, or analytical parameters.
- **Integration into laboratory-developed testing** – establishing reliability when IVD components are combined with other reagents, software, or systems to form a modified or composite test process.
- **Use of Research Use Only (RUO) reagents** – ensuring that RUO-labelled materials incorporated into diagnostic testing are subject to full validation before being applied to clinical service, as they fall outside the scope of manufacturer claims for diagnostic use.
- **Extension of principles to emerging technologies** – applying the same risk-based and evidence-driven validation framework to novel diagnostic tools, including AI-driven laboratory systems, digital pathology platforms, and other innovations.

The document does not prescribe specific experimental protocols or statistical methods; rather, it provides a principles-based framework for planning, executing, and documenting validation activities in alignment with ISO 15189 requirements for quality management, technical competence, and patient safety. It is intended for use by laboratory directors, quality managers, and technical staff responsible for ensuring that all diagnostic methods, regardless of regulatory status, are demonstrably fit for purpose in the context of their own laboratory environment.

This guidance does not apply to companion diagnostic devices or IVDs that are manufactured and used exclusively for clinical trials.

ISO 15189 requirements

Medical laboratories accredited to ISO 15189 are required to comply with all applicable clauses of the standard, ensuring both the quality and competence of their services. Validation and verification activities are a key component of this compliance, underpinning the reliability of patient results and the credibility of the laboratory's operations.

Validation-specific clauses

ISO 15189 contains explicit requirements for the validation and verification of examination procedures, particularly within Clause 7 (Examination processes). Laboratories must:

- Verify that examination procedures provided by manufacturers perform as intended under the laboratory's specific conditions (Clause 7.3.2).
- Validate examination procedures developed or modified by the laboratory, or those used outside their intended scope, to ensure suitability for the intended clinical purpose (Clause 7.3.3).
- Document the validation or verification process, including the study design, acceptance criteria, results, and conclusions, in a manner that is transparent, reproducible, and auditable.

Associated clauses in authorisation and measurement uncertainty

In addition to the validation-specific clauses, several other ISO 15189 requirements are closely linked to validation activities:

- **Authorisation of examination procedures (Clause 7.3.2 and 7.3.3):** Laboratory management must formally authorise any validated or verified examination procedure before it is placed into routine use. Authorisation requires documented evidence of satisfactory performance and alignment with clinical needs.
- **Estimation of measurement uncertainty (Clause 7.3.4):** Where quantitative results are reported, laboratories must determine and document the measurement uncertainty associated with each procedure. Validation studies should generate data that contribute to this estimation, ensuring results are both accurate and appropriately qualified.
- **Ongoing monitoring (Clause 7.3.1e):** Validation is not a one-off exercise. Laboratories must have systems in place for ongoing performance monitoring, including quality control, external quality assessment, and periodic review, to confirm that methods remain valid over time.

By integrating these clauses into a coherent validation strategy, laboratories can ensure not only compliance with ISO 15189 but also a robust quality framework that supports patient safety and clinical decision-making.

General Principle of Validation

Validation is the process by which a laboratory demonstrates that an examination procedure is fit for its intended purpose in its own operational environment. While the specific requirements will vary depending on the context, the underlying principle is always the same: patient results must be reliable, accurate, and clinically meaningful.

Validation procedures for each IVD must generate clinically relevant evidence against a superior standard. Clinical evidence means data derived from studies that use relevant patient samples, in a clinical setting, using the trained users that operate the IVD and meeting acceptance criteria.

When is validation needed?

Validation is required whenever there is any change, uncertainty, or deviation from an established, approved, or previously validated method. Common scenarios include:

- Tests and methods developed in-house (i.e. within the health institution) – incl. procedures designed and optimised entirely within the laboratory.
- Commercial IVDs used outside the manufacturer's IFU – e.g., alternative sample types, modified workflows, or analytical parameters.
- Adaptation of existing methods – e.g., change in instrumentation, reagents, or software algorithms.
- Use of Research Use Only (RUO) reagents – since RUO-labelled products have no manufacturer claims for diagnostic performance, they must be treated as equivalent to in-house methods and subjected to **full validation** before clinical implementation.
- Implementation of new technologies – including AI-based decision support tools, digital pathology systems, and molecular platforms not yet covered by standard guidance.

Practical considerations – "How much is enough?"

The depth and extent of validation should be proportionate to the risk posed by potential method failure. Factors influencing the scope of validation include:

- Novelty of the method – entirely new procedures require more extensive assessment than minor modifications.
- Criticality of the measurand – tests with high clinical impact (e.g., those guiding life-critical decisions) demand more rigorous validation.
- Risk of harm – where incorrect results could cause significant patient harm, validation should be more comprehensive.

- Existing evidence base – well-established methods with extensive published data may need less local testing.

In practice, laboratories should adopt a risk-based approach. If patient safety or result reliability could be compromised, the validation should be sufficiently thorough to mitigate that risk. Risk assessment should follow recognised standards such as ISO 22367 and, where appropriate, ISO 14971, ensuring that hazards are identified, risks are estimated, and mitigation measures are documented and justified for the intended clinical use.

Because proportionality of risk is inherently subjective, laboratories should use structured and recognised frameworks to guide decision-making. In the UK, the MHRA's risk classification guidance for medical devices and IVDs provides a consistent basis for assessing and documenting proportionality of risk (MHRA Borderline Products and Risk Classification Guidance). This categorises IVDs into General, Self-testing, Annex II List B, Annex II List A or classes A–D, reflecting increasing levels of risk, and can be applied to determine the extent of validation required. Aligning local validation practice with this classification system ensures that risk-based decisions are transparent, reproducible, and defensible during accreditation and regulatory compliance.

Using external data to reduce local validation burden

ISO 15189 recognises that laboratories may use validation data generated by other accredited sites or peer-reviewed sources, provided they assess its relevance. Before relying on external data, consider:

- Patient cohort comparability – are the population demographics, prevalence rates, and disease patterns similar to those in your laboratory's service?
- Environmental and operational differences – variations in sample type, instrumentation, reagents, staff expertise, and environmental conditions may affect performance.
- Regulatory and accreditation status of the source – data from accredited laboratories following recognised standards carries greater weight.

If external evidence is robust and relevant, local validation can be adjusted to confirm critical performance parameters rather than repeating full validation. This may be particularly required for validation of point of care testing (POCT) devices where no comparable laboratory method exists. There is still a requirement for documentation of the rationale for reduced testing and demonstration that risks have been addressed.

If performance specifications aren't met

When validation shows that an examination procedure fails to meet predefined acceptance criteria, the laboratory must follow a structured process:

1. Assess the nature and impact of the deviation – determine whether the shortfall affects clinical interpretation or patient safety.
2. Apply risk management principles (ISO 22367) – identify hazards, estimate risks, and evaluate whether they are acceptable or require mitigation.
3. Decide on actions – options include adjusting acceptance criteria (if clinically justifiable), modifying the method, sourcing alternative procedures, or rejecting implementation altogether.
4. Document decisions – maintain a full audit trail of findings, risk assessments, and justifications for the chosen course of action.

By applying these principles consistently, laboratories can ensure that all examination procedures, whether purchased, adapted, or developed in the laboratory, are demonstrably fit for purpose, compliant with ISO 15189, and aligned with the patient safety focus of ISO 22367.

Practical Validation Workflow

The following stepwise workflow provides a structured approach to validation and verification activities in medical laboratories, mapped to relevant ISO 15189 requirements. While the scope of each step will vary depending on the complexity of the method and the degree of deviation from the manufacturer's instructions, the underlying principles remain constant.

Note: ISO 5649 provides additional guidance on validation processes.

1. Define the Scope and Intended Use
    - *Relevant clauses: 7.3.1, 7.3.2, 7.3.3*
    - Clearly describe the examination procedure, its intended clinical purpose, and any modifications or "off-label" applications.
    - Identify the patient population, sample types, analytical range, and expected clinical context.
2. Risk Assessment
    - *Relevant clauses: 5.6 (Risk management), 8.5 (Actions to address risks and opportunities for improvement), 7.1*
    - Evaluate potential risks to patient safety and result reliability if the procedure does not perform as expected.
    - Use a risk-based approach to determine the extent of validation required.
3. Develop a Validation Plan
    - *Relevant clauses: 7.3.3, 8.3 (Document control), 8.4 (Control of records)*

- Define performance characteristics to be assessed (e.g., accuracy, precision, sensitivity, specificity, linearity, carryover, limit of quantification).
- Establish acceptance criteria based on clinical requirements, manufacturer claims, and regulatory guidance.
- Specify sample numbers, control materials, statistical methods, and environmental conditions for testing.

4. Conduct Validation/Verification Studies
    - *Relevant clauses: 7.3.2, 7.3.3*
    - Execute the study plan approved in pre-defined methods using representative patient samples and/or appropriate quality control materials.
    - Capture all data in a controlled, traceable format.
5. Analyse and Interpret Data
    - *Relevant clauses: 7.3.3, 7.3.4*
    - Compare observed performance against acceptance criteria.
    - Where applicable, use validation data to support the estimation of measurement uncertainty for quantitative results.
6. Document Findings and Authorise Use
    - *Relevant clauses: 7.3.3, 8.3, 8.4*
    - Compile a comprehensive validation report including study design, raw data, statistical analyses, conclusions, and recommendations.
    - Add residual risks and validation conclusions into the instructions for use
    - Obtain formal authorisation from laboratory management before introducing the method into routine service.
7. Implement and Monitor in Routine Use
    - *Relevant clauses: 7.3.2e (Ongoing monitoring), 8.7 (Corrective actions)*
    - Integrate the validated method into standard operating procedures.
    - Monitor performance via internal quality control, external quality assessment, and periodic review of measurement uncertainty.
    - Re-validate if significant changes occur in reagents, equipment, software, or intended use.

This workflow is applicable not only to IVDs used within or outside their IFU, but also to IVDs that have been developed in the laboratory. It also applies to emerging diagnostic technologies such as AI-assisted systems, where performance must be demonstrated under the laboratory's specific operating conditions before results are used for patient care.

Quick-Reference Validation Requirements Matrix

Scenario	Minimum Validation Requirement	Key Considerations	Relevant ISO 15189 Clauses	ISO 22367 Link
Health institution developed method	**Full validation** of all relevant performance characteristics (accuracy, precision, sensitivity, specificity, reportable range, limit of quantification, robustness, measurement uncertainty)	No manufacturer data; design acceptance criteria based on clinical need; high documentation burden	7.3.3, 7.3.4, 8.3, 8.4	Full risk assessment before implementation
Commercial IVD used per IFU	Verification of manufacturer claims for accuracy, precision, reportable range, and MU	Match IFU conditions; confirm performance in local environment and patient population	7.3.2, 7.3.4	Risk assessment if any performance claim is marginally met
Commercial IVD used outside IFU (off-label)	**Full validation** as for health institution method	Assess impact of changes (sample type, workflow, cut-off values); check regulatory implications	7.3.3, 7.3.4	Risk analysis of harm from modified use
Change in instrumentation/ reagents/software	Partial validation focused on parameters potentially affected	Compare with baseline data; confirm comparability; monitor post-implementation	7.3.2	Evaluate risk of analytical or interpretive differences
New technology or emerging platform (e.g., AI-assisted laboratory tool)	Validation of performance claims and additional assessment for interpretive reliability	Include usability, algorithm stability, and output reproducibility; ethics and bias considerations	7.3.2, 7.3.3, 7.3.4	Full risk assessment covering patient safety and decision-making impact

Scenario	Minimum Validation Requirement	Key Considerations	Relevant ISO 15189 Clauses	ISO 22367 Link
Use of external validation data	Local verification of key parameters only	Assess relevance of cohort, conditions, and quality of external study; document justification	7.3.2, 7.3.3	Determine quality and appropriateness of the external data
Use of Research Use Only (RUO) reagents	**Full validation** as for health institution method	RUO-labelled products have no diagnostic performance claims; must not be assumed equivalent to CE/UKCA IVD kits	7.3.3, 7.3.4	Mandatory risk assessment due to lack of manufacturer validation

Glossary (taken from ISO 15189:2022)

- **examination**
  set of operations having the objective of determining the numerical value, text value or characteristics of a property

  Note 1 to entry: An examination may be the total of a number of activities, observations or measurements
  required to determine a value or characteristic.

  Note 2 to entry: Laboratory examinations that determine a numerical value of a property are called "quantitative examinations"; those that determine the characteristics of a property are called "qualitative examinations".

  Note 3 to entry: Laboratory examinations are also called "assays" or "tests".

- **examination procedure**
  specifically described set of operations used in the performance of an *examination* according to a given method

  Note 1 to entry: In the IVD medical device industry and in many laboratories that use IVD medical devices, an examination procedure for an analyte in a biological sample is commonly referred to as an analytical method, analytical procedure or test procedure.

- **in vitro diagnostic medical device (IVD medical device)**
  device, whether used alone or in combination, intended by the manufacturer for the *in vitro* examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes and including reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles

Appendices with specific examples

- Case Study 1: Validation of Self-Taken Swabs for CT/GC
- Case Study 2: Validation of Blood Spot 17-hydroxyprogesterone (17OHP) Assay
- Case Study 3: Validation of routine chemistry assay using blood collected from an upper arm capillary collection device
- Case Study 4: Validation of a Research Use Only Next Generation Sequencing Gene Panel for Solid Tumours

Case Study 1: Validation of Self-Taken Swabs for CT/GC

Data collected in a diagnostic microbiology laboratory in the UK.

Rationale

- During the COVID-19 pandemic, face-to-face clinic attendance was significantly restricted.
- Traditional clinician-taken swabs were not always possible, creating a need for self-taken samples to maintain STI diagnostic services.
- Use of self-taken rectal, throat, and urethral swabs on the Hologic Panther Aptima Combo 2® assay and GC confirmation on the Cepheid GeneXpert® CT/NG assay was outside the manufacturers' Instructions for Use (IFU).
- Therefore, validation was required before introducing this off-label application into routine clinical practice.

Method

- A prospective validation study compared paired self-taken and clinician-taken swabs from rectal, throat, and urethral sites.
- Acceptance criterion: ≥95% concordance between self- and clinician-taken samples.

Supplementary retrospective analysis ensured sufficient numbers of positive CT and GC throat samples were included.

Outcome

- Rectal swabs: 155 paired samples tested; >95% concordance for both CT and GC.
- Throat swabs: 243 paired samples tested; >95% concordance for both CT and GC. Additional retrospective testing achieved target positivity rates (10% CT, 13% GC). Concordance: 96% for CT, 97% for GC.
- Urethral swabs: 20 clinician-taken samples tested on GeneXpert; all Panther positives confirmed.

Lessons Learned

- Self-taken throat and rectal swabs are a suitable alternative to clinician-taken swabs for the detection of CT and GC, achieving >95% concordance.
- Off-label use requires local validation, even where the platform and assay are CE-marked.

- Retrospective data can strengthen validation where prospective sample positivity rates are lower than expected.
- This example demonstrates how laboratories can rapidly adapt service delivery under exceptional circumstances, while maintaining compliance with ISO 15189 validation principles and ensuring patient safety.
- Data obtained can be provided to the manufacturer to support post market surveillance clinical follow-up.

Case Study 2: Validation of Blood Spot 17-hydroxyprogesterone (17OHP) Assay

Data collected in a diagnostic biochemistry laboratory in the UK.

Rationale

- Children with classical congenital adrenal hyperplasia (CAH) require lifelong hormone replacement therapy with glucocorticoids and sometimes mineralocorticoids.
- Optimal dosing of hydrocortisone in paediatrics can be challenging. Too little can lead to androgen excess and can impact normal growth and puberty, whereas too much can also stunt growth and cause weight gain.
- To mimic the diurnal HPA axis, patients with CAH should take hydrocortisone three times per day.
- Monitoring of treatment can be performed by the patient (or parent) by taking blood spot samples throughout the day, usually before taking a hydrocortisone dose, and sending them to the laboratory for analysis. These blood spot 17OHP concentrations can help guide treatment.

Method

- The assay was developed on a Waters TQSmicro mass spectrometer, and a full validation was performed. This included precision, LLOQ, linearity, carryover, recovery, interference studies, post extraction stability and ion ratios. In addition, EQA material was analysed, and two method comparisons performed. One compared results with a previously developed blood spot LC-MS method and the other compared results with a blood spot immunoassay method.
- Blood spot 17OHP calibrator material was prepared in the health institution by spiking 17OHP certified reference material into discarded red cells provided by the transfusion lab. This spiked blood was then spotted onto blood spot cards.
- Blood spot samples were reviewed post-analysis. If they were of poor quality the results were not reported as they will not be accurate.

Outcome

- Patients collect the blood spot samples and send them to the laboratory in the post. The lab analyses the samples prior to the monthly paediatric CAH clinic. This allows the paediatric endocrinologists to optimise hydrocortisone dosing at the clinic appointments.

- Health institution blood spot calibrators can be successfully made in the health institution. However, this increases the importance of using third party QC material as well as having access to an accredited EQA scheme.

Lessons Learned

- Blood spot assays are less precise than compared with plasma/serum. Be aware of this when writing the validation specification.
- Poor blood spot quality is the most likely reason a result is not reported. The lab has worked with the paediatric endocrine team to provide guidance as to how to take a good blood spot to improve the blood spot quality.

Case Study 3: Validation of routine chemistry assays using blood collected from an upper arm capillary collection device.

Data collected in a diagnostic biochemistry laboratory in the UK.

Rationale

- Patients with learning disabilities could be needle phobic and are unable to provide routine venepuncture blood samples.
- This leads to missed annual health checks/medication monitoring and increased morbidity and early mortality in this population (LeDeR report 2025).
- Use of capillary blood for measurement of routine chemistry analytes on Beckman Coulter DxI800 and AU5800 automated platforms was outside the manufacturer's Instructions for Use (IFU). HbA1c using the TOSOH G11 was assessed using capillary vs venepuncture collections.
- Validation of capillary blood used to obtain serum for measurement was required before introducing this off-label application into routine clinical practice.

Method

- A validation study compared paired supervised collection of capillary samples and clinician-taken, routine venepuncture blood samples. Samples were delivered to the laboratory by scheduled van collection at the GP practice (maximum of 6 hours between sample collection and delivery to lab).
- Minimal total serum volume presented to the DxI800 and AU5800 (also off-label application) was established by 5 x 5 x 5 imprecision assessment using Internal Quality Control Material and pooled patient serum. This was to maximise the number of tests obtained from small capillary collections.

Outcome

- Concordant results were obtained for most main chemistry analytes except potassium, which had a significant positive bias. Bone profiles, liver function tests and lipid profiles all showed > 95 % concordance as did HbA1c.
- Immunoassay tests for thyroid function, haematinics, prolactin and cortisol were all with 95 % limits and total sample volume presented to the DxI800 immunoassay platform was reduced by up to a third, thus maximising use of small serum samples.
- A pilot study of 20 patients with LD and needle phobia in a GP practice environment demonstrated 100 % acceptability and painless experience by the patient and an end-to-end service from test requesting, sample collection to result back to GP record.

Lessons Learned

- Supervised collection of upper arm capillary blood samples provides a reasonable adjustment for patients with learning disabilities and needle phobia. Sampling can take place wherever is convenient and comfortable for the patient.
- Off-label use requires local validation to establish concordance with standard venepuncture samples. Samples collected by capillary collection should be flagged in the patient record to provide trending data over time.
- This example demonstrates how routine laboratories can adapt service delivery to enable equity of access for patients who struggle to give standard venepuncture blood samples.

Case Study 4: Validation of a Research Use Only Next Generation Sequencing Gene Panel for Solid Tumours

Data collected in a diagnostic genomics laboratory in the UK.

A number Best Practice Guidelines and papers for Next Generation Sequencing Validation have been published, in addition to Mattocks et al (2010) A standardised framework for the validation and verification of clinical molecular genetic tests.

Rationale

- The diagnosis, prognosis and treatment of cancer may be influenced by the variations in genomic sequence seen in tumour samples.
- Testing on DNA extracted from Formalin Fixed Paraffin Embedded (FFPE) tissue can be challenging and as the number and complexity of tumour related target sequences increase, methods to identify increasing numbers of targets in a timely manner become important.

Method

- A research use only (RUO) assay for detection of small nucleotide variants by next generation sequencing (NGS) on solid tumour samples was validated for diagnostic use.
- DNA from FFPE tumour samples of known genotype were prepared and run on the NGS panel together with commercial controls and EQA samples. The total number of samples was 46.
- Sequence data was run through a bioinformatic pipeline and analysis performed to confirm coverage of target regions and assess detected variants.
- NGS Panel runs were compared for intra- and inter-run compatibility, assessing sensitivity, specificity and limits of detection for the assay.
- The types of variants detected were compared to ensure variants of differing complexity were identified.
- Results were reviewed to assess the minimum concentration of DNA required for the assay.
- Data was compared with previous results obtained from validated, traceable, ISO15189 accredited methods; with statistical analysis performed to ensure comparability of successful runs.
- The limits of detection, uncertainty of measurement and minimum gene coverage for variant detection were identified.

- Ongoing verification continues using commercial controls at a specified timeframe.

Outcome

- A validated test is now provided for variants detected at or above a 5% Variant Allele Frequency (VAF).
- The test has improved efficiency and enables increased numbers of sequences of interest to be identified.

Lessons Learned

- Robust variant detection requires a variant calling of above 5%; with a minimum 20% tumour content minimum improving detection.
- The test has been validated for sequence variants, but additional independent validation may enable extension of testing to include Copy Number Variants (CNV).
- The extent of validation and verification for a more complex panel would involve greater numbers of samples to ensure compliance with requirements.

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