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RISK-BASED AUDITING APPROACH

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N.B. This OMCL Quality Management System document is applicable to members of the European OMCL Network only. Other laboratories might use the document on a voluntary basis. However, please note that the EDQM cannot treat any questions related to the application of the documents submitted by laboratories other than the OMCLs of the Network.

1. INTRODUCTION

The overall common objective of the European Regulatory Network is to ensure the health and well-being of patients and protect public health through medicinal products of high quality that are safe and effective. OMCLs contribute to this objective by testing the quality of medicines on the market (legal or illegal) and by producing reliable test results as a basis for adequate decision-making by the competent authority. However, risks to patients or to public health can often only be estimated within a specific context. This Guidance therefore focuses on the risks to the validity of reported test results.

Application of a risk-based approach in auditing is primarily aimed at the identification of risk factors. This includes the careful selection of methodologies that are representative of the laboratory's scope to ensure confidence in the conformity of the laboratory with the requirements of ISO/IEC 17025, OMCL Guidelines and the Ph. Eur. This risk-based identification and selection should follow a structured approach for planning and conducting audits. It should also be applicable to all laboratories and include additional ad hoc elements, e.g. randomly selected and/or new topics under the scope.

2. OBJECTIVE AND SCOPE

The purpose of this Guidance is to define criteria for the identification of risk factors during technical audits and the risk-based selection of methods or techniques in cases where the full scope cannot be assessed with the available audit capacity. A risk-based reduction of the technical scope is aimed at ensuring confidence in the laboratory's ability to meet the requirements while balancing the elements of the scope and the audit time frame available (for criteria and examples refer to section 6). Moreover, adequate identification of the risk factors that contribute to the validity of results is key to ensuring that the laboratory is in control of its various elements.

This Guidance can support the audit team in the preparation of the MJA schedule, whenever the concept of risk-based auditing becomes necessary. The Guidance does not have a prescriptive character.
Application of a risk-based approach in audits is focused on identifying risk-based methodologies to attain the necessary confidence of the conformity of the lab with the requirements of ISO/IEC 17025, OMCL Guidelines and Ph. Eur. requirements.

Reduction of the scope of the technical audit should not be applied in cases where the full scope can be covered within the normal time frame (usually two days of assessment). However, in the event of a large scope involving different lab units and/or a wide instrument park, the considerations presented in this Guidance should be taken into account during the preparation of the audit schedule.

Regarding the quality system, all clauses of ISO/IEC 17025 shall be covered in an audit; therefore the quality system is out of the scope of this document.

3. DEFINITIONS/GLOSSARY

Audit scope: extent and boundaries of an audit.
Audit criteria: reference against which conformity is determined, e.g. applicable standard, policies, procedures, regulatory requirements, performance criterial including objective.
Risk-based approach: an audit approach that considers risk and opportunities. The risk-based approach should substantively influence the planning, conducting and reporting of audits in order to ensure that audits are focused on matters that are significant for OMCL function.

4. METHODOLOGY FOR RISK-BASED AUDITING APPROACH

All relevant risk factors that apply to a specific OMCL shall be covered during an audit. As long as the laboratory follows a structured approach and employs a high level of standardisation across different fields of expertise or organisational units (if applicable), a spot check with positive outcome for each risk factor should be sufficient to assure compliance. On the other hand, if the audit team uncovers indications that an approach is not standardised, the sample should be expanded.

For the audit of the quality system, all clauses of ISO/IEC 17025 shall be covered in an audit.

For the technical audit, this Guidance identifies several typical risk factors that shall be addressed during an audit. The list of risk factors provided in section 6 should not be considered exhaustive, and not all risk factors are applicable to all OMCLs.

5. METHOD-SPECIFIC RISK FACTORS: GROUPING OF TEST METHODS

Several of these risk factors are related to specific analytical techniques. Therefore, test methods may be grouped in order to select an item out of every cluster, while other risk factors are independent of the analytical technique.

Some examples are provided for clarification:

1. An OMCL uses two LCs, i.e. LC1/DAD and LC2/MS. Providing that both are under the same QMS, once qualification is successfully verified for LC1, it would not be re-checked for LC2. Both detectors will be audited in full.
2. Several chromogenic assays of coagulation factors may be covered by auditing only one method, given that they follow a common approach in validation, assay layout, equipment and staff involved.

These method clusters are identified in Table 1.

Table 1-Method Clusters

Main method/technique	**Cluster**	**Risk factors that require selection of more than one sample out of the cluster**
Chromatography	GC	• all types of detectors in use (incl. MS) • all different separation modes
	TLC	• all types of detection methods (e.g. chemical, visual, etc.)
	HPLC/UPLC	• all types of detectors in use (incl. MS) • all different separation modes (reversed phase, normal phase, ion exchange, SEC, etc.)
Electrophoresis	SDS-PAGE	
	Blotting	
Physical	Dissolution test	• different dosage forms/apparatus
	Gravimetry	• different precision requirements
	Volumetry	• excl. volumetric titration (see below)
Visual determination	Appearance	• incl. semi-quantitative determination of coloration/opalescence
	Optical microscopy	
Spectrometry	Atomic (AAS/AES/ICP)	• different modes of atomisation
	Fluorimetry	
	IR/NIR/Raman	• different types of sample preparation/measurement modes
	MS	• all types of ionisation modes/analysers in use
	UV/Visible	
Titration	Visual endpoint	• all types of titration
	Potentiometric	• all types of titration
	Simple identification of ions with visual determination	

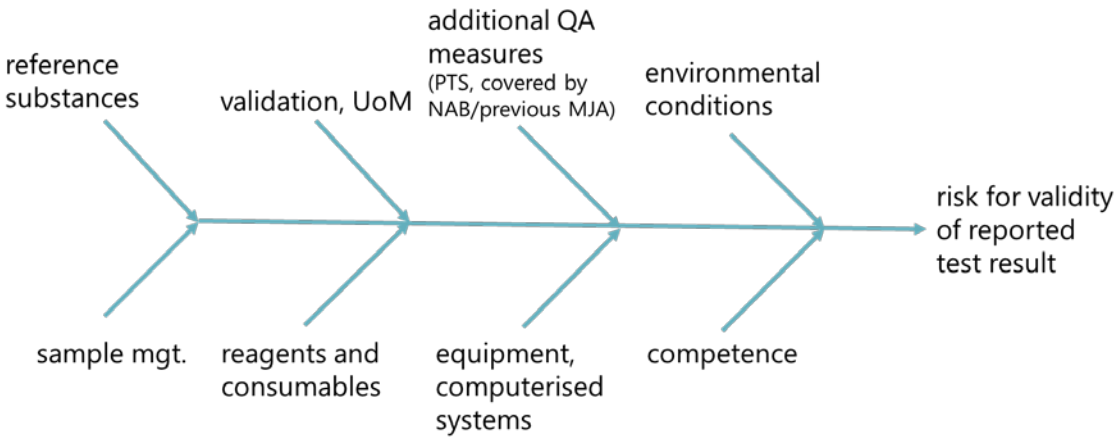
Main method / technique	Cluster	Risk factors that require selection of more than one sample out of the cluster
Immunochemical methods	Immunoassay (ELISA)	• self-prepared plates • validation of anti-HIV & HBsAg in pool plasma
Coagulation	Chromogenic	
	Clotting time	
Vaccine potency	Virus titration	• all detection techniques in use (visual, staining, antibody staining, NAT, etc.)

6. GENERAL (METHOD-INDEPENDENT) RISK FACTORS FOR THE VALIDITY OF TEST RESULTS

Other risk factors mentioned in this Guidance are independent from the analytical techniques. Therefore, effective communication between the technical auditors is essential in order to cover all relevant items in an audit without overlap/duplication.

Risk factors that contribute to the validity of reported test results are depicted in the fishbone diagram below and further discussed in Table 2, including the points to be checked during the audit. The list below is not comprehensive and, unless indicated, is not given in priority order.

Fig. 1 Fishbone diagram of general risk factors:



The management of these and some additional risk factors are addressed by OMCL Quality Management Guidelines or Recommendation Documents.

Table 2. Risk factors that contribute to the validity of reported test results and points to be checked during the audit.

General Risk Factors	References	Check
Equipment	GL Qualification of Equipment & Annexes	• All types of equipment shall be audited • Check specific requirements (as audit criteria) defined by Ph. Eur. or GLs, as applicable • For widely used equipment (pipettes, balances, refrigerators, etc.), spot-check if they are consistently managed across the OMCL. If not, expand sample
Reference Substances	GL Handling and Use of Non-Compendial Reference Standards in the OMCL Network	• Reference substances obtained from marketing authorisation holders (MAH) • Reference substances obtained by purchasing from commercial sources • Use of reference substances outside the intended scope (e.g. storage and re-use of aliquots) • Secondary in-house reference substances established by the OMCL
Reagents	GL Management of Reagents	• Purchased reagents in their original container • Purchased reagents which have been transferred into another container • In-house prepared reagents • Water manufactured by the OMCL using qualified equipment • Volumetric solutions
Validation	GL Validation/Verification of Analytical Procedures	• Prioritise according to complexity of validation requirements: - impurity quantitative > assay > impurity limit > identification - full validation (in-house) > partial validation (e.g. active substance method for finished product, 2nd manufacturer's method) > verification of fully validated method • Check if verification/SST requirements are systematically checked and fulfilled • Check changes in the method and validation status of the method
	GL Evaluation of Measurement Uncertainty	• In-house developed methods • Ad hoc methods (e.g. screening, analysis of unknown products, trace analysis) • Methods with unknown or incomplete information regarding uncertainty • Confirming out-of-specification results • Identification of uncertainty sources
Computerised systems	GL Computerised Systems & Annexes	• Management of installation and updates of (commercial) equipment software • Self-developed Excel spreadsheets • Complex systems (LIMS validation)

General Risk Factors	References	Check
Environmental conditions	Recommendation Document Management of Environmental Conditions	Method-specific audit items, as applicable: • Temperature: storage and environmental conditions (samples, reagents and reference substances) • Specific temperature requirements (e.g. drying, ash, microbiological incubation) • Vibrations: weighing, LAL • Cross contamination & hygiene in general: NAT & microbiology (incl. particle count and differential pressure in clean rooms) • Light & humidity: animal house
Sample Management	GL Management of Samples	Prioritisation acc. to risk factors from matrix/required sample preparation: • unknown > complex (e.g. ointments, herbals) > solution • product-specific storage conditions
Competence requirements	Qualification and Requalification of Analysts General Requirements for Infrequently performed techniques	• Recently introduced new staff • Recently introduced methods (incl. training) • Systematic approach to infrequently performed techniques • Method-specific risk factors from specific/complex handling requirements • Re-qualification programme
Ensuring validity of results	ISO/IEC 17025 7.7 (no additional OMCL requirements)	• PTS participation (see last management review) and failure management • Laboratory comparisons other than PTS (collaborative studies) • Use of Control charts • Blind samples Triggers for method selection: • No PTS participation or poor PTS performance • Not covered by NAB accreditation • Not covered by previous MJA • Other approaches

General Risk Factors	References	Check
Evaluation and reporting of results	GL Evaluation and reporting of results GL Management of documents and records ISO/IEC 17025 clause (clause 7.8)	• Traceability of technical records (including calculations, transcription and checks). • Decision rules in case of conformity assessment • OOS Verification/investigation/decisions and effectiveness of actions • Test reports • Interpretations and decisions based on test results (assessment, OCABR certificates, etc.)

7. RESPONSIBILITIES

The audit team is responsible for the risk-based selection of audit items.

However, the audited laboratory should contribute by providing the necessary information to support a meaningful method selection during the preparation phase, when applicable.

Risk-based selection of the methods will be defined before the audit, and any change discussed/agreed with the audited lab.

8. REFERENCES

1) ISO 19011:2018 for auditing management systems, clauses 4.g), 6.3.2.1., 6.3.2.2.h)
2) ISO/IEC 17025:2017 General requirements for the competence of testing and calibration laboratories
3) OMCL Quality Management Guidelines and Recommendation Documents