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Ensuring reliable and accurate results of analytical processes

Ensuring Validity of Examination Results

What is new in the new ISO 15189

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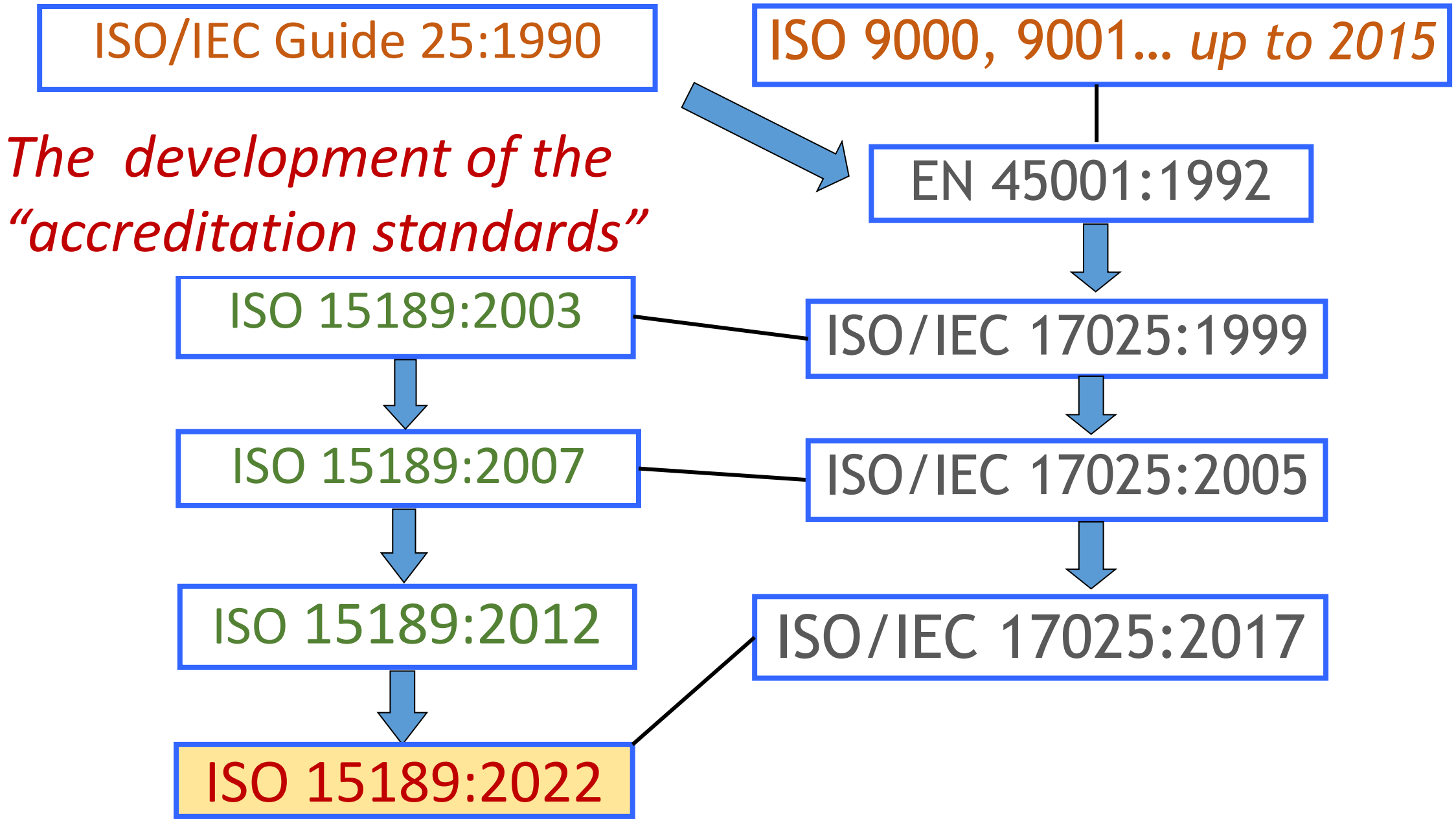
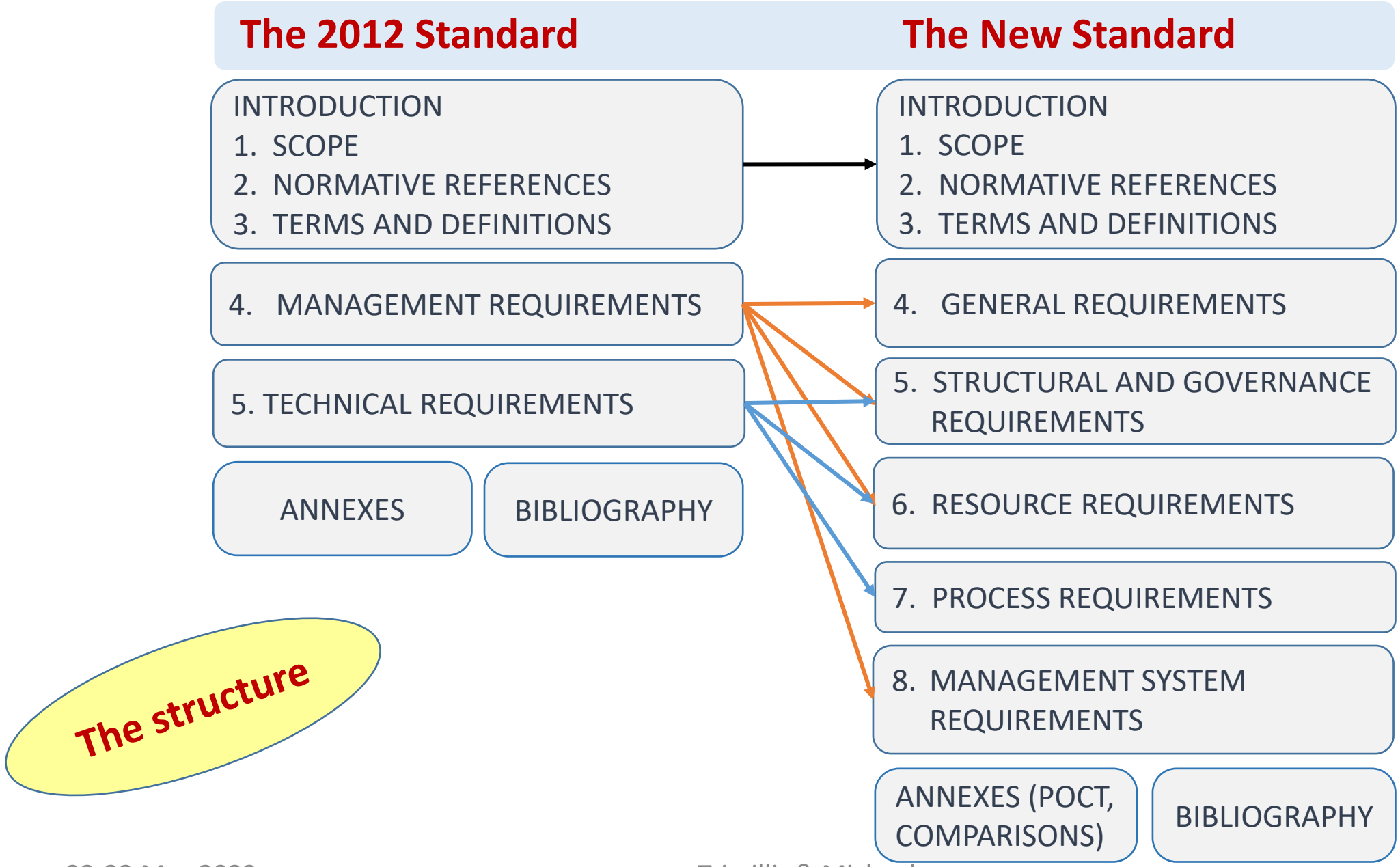

ISO/IEC Guide 25:1990
ISO 9000, 9001… up to 2015
The development of the "accreditation standards"
EN 45001:1992
ISO 15189:2003
ISO/IEC 17025:1999
ISO 15189:2007
ISO/IEC 17025:2005
ISO 15189:2012
ISO/IEC 17025:2017
ISO 15189:2022

Important terms

- biological reference interval
- clinical decision limit
- commutability of a reference material
- external quality assessment
- in vitro diagnostic medical device
- internal quality control
- laboratory user – patient
- calibrator/calibration material
- control material
- Certified Reference Material (CRM)
- Reference Material (RM)

What is changing?

- ❑ The structure: follows the format of new ISO/IEC 17000 series
- ❑ The terminology (ref. to new standards/guides or their new versions)
- ❑ The introduction of some new provisions
- ❑ Risk and opportunities
- ❑ The management system (including two alternatives)
- ❑ No requirement for a Quality Manual, no reference to Technical/Quality Manager
- ❑ Procedures Vs processes – More flexibility
- ❑ Requirements for point-of-care-testing (POCT)


The 2012 Standard
The New Standard
INTRODUCTION
1. SCOPE
2. NORMATIVE REFERENCES
3. TERMS AND DEFINITIONS
4. MANAGEMENT REQUIREMENTS
5. TECHNICAL REQUIREMENTS
ANNEXES
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6. RESOURCE REQUIREMENTS
7. PROCESS REQUIREMENTS
8. MANAGEMENT SYSTEM REQUIREMENTS
ANNEXES (POCT, COMPARISONS)
BIBLIOGRAPHY
The structure

The definition for the medical laboratory

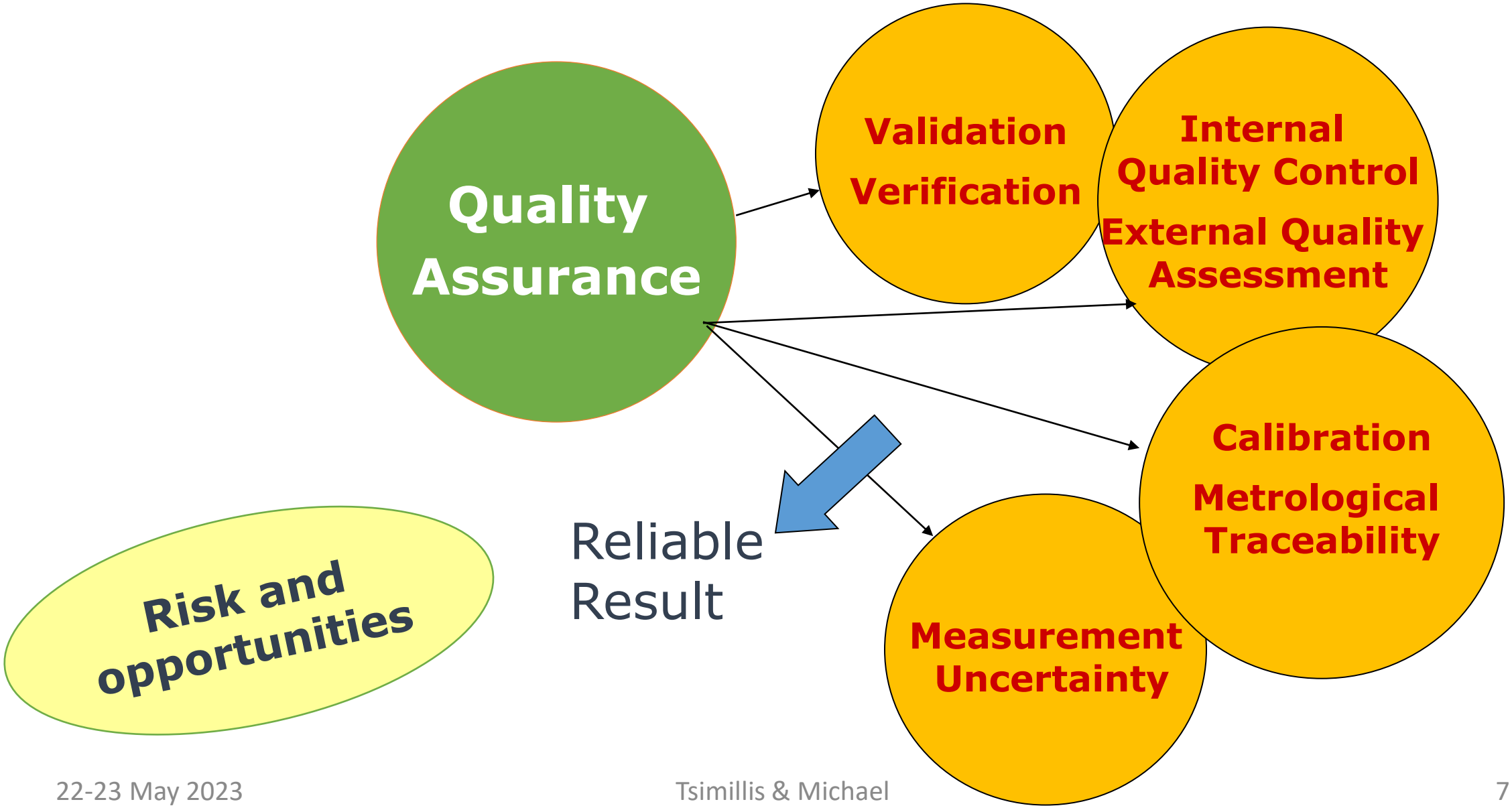
§ 3.20 : Entity for the examination of *materials derived from the human body* for the purpose of providing information for the diagnosis, monitoring, management, prevention and treatment of disease, or assessment of health

Note 1: *provision of advice covering all aspects of examinations incl. appropriate selection, interpretation of results and advice for further examinations*

Note 2: *activities include pre-examination, examination and post-examination processes*

Note 3: *examples of materials: microbiological, immunological, biochemical, immunohaematological, haematological, cytological, tissue and cells and genetic material*

Ensuring the validity of results…



Potential risks to patient care…

during all processes, i.e. pre-examination, examination and post-examination…

➢ *The laboratory shall*

- assess and mitigate the risks "to the extent possible" and communicate the residual risk to the users
- monitor and evaluate risks and effectiveness of their mitigation according to the potential harm to the patient
- identify opportunities to improve patient care

Risks and opportunities

Risk is…

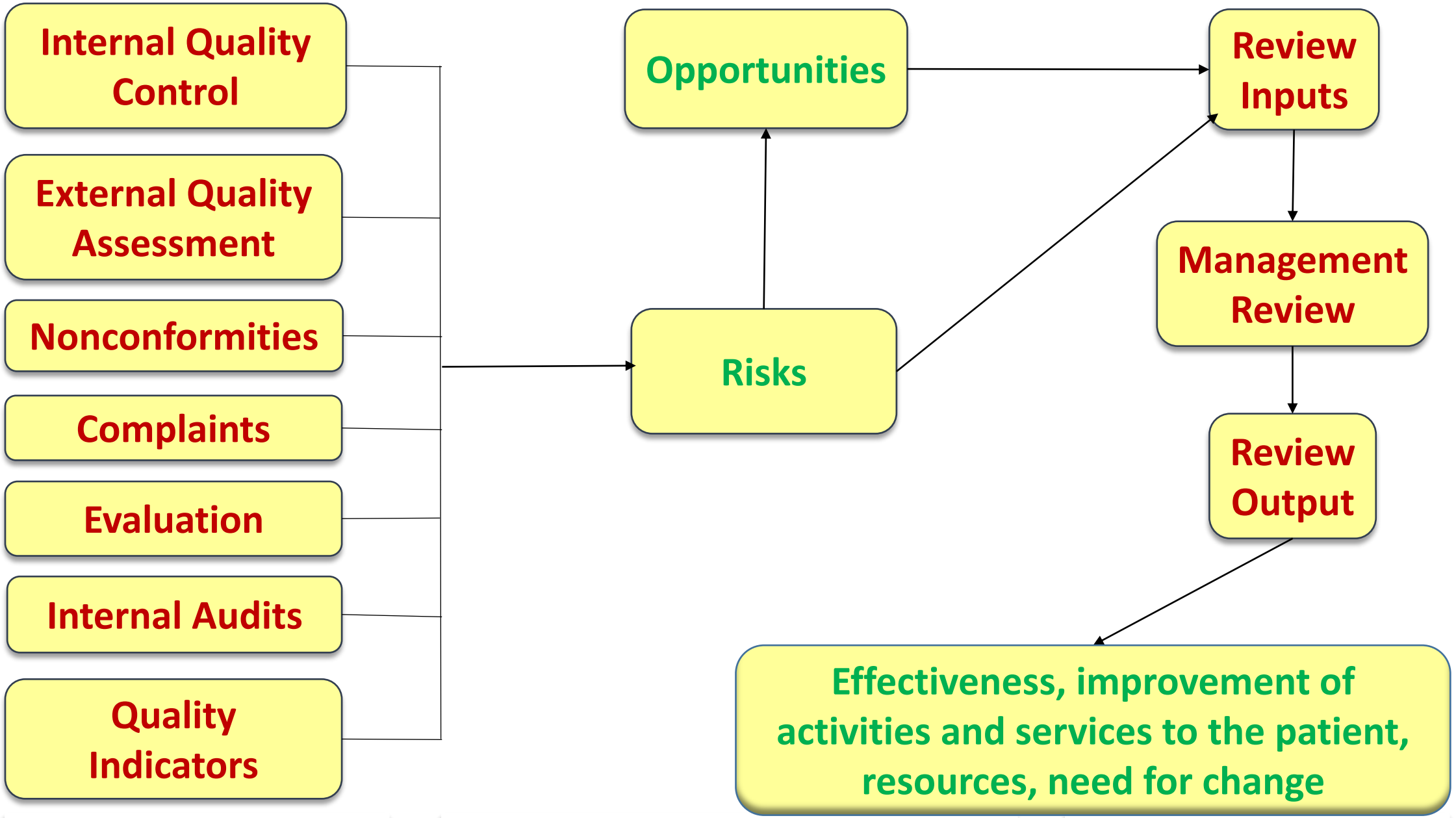
- the effect of uncertainty on the achievements *(Guide ISO 73:2010, definition 1.1*), **OR**
- the combination of the probability of occurrence of harm and severity of the harm *(ISO/IEC Guide 51:2014, definition 3.9)*

➔*Is risk of importance?* Two figures provide an illustrative answer:

There are 85 references to risk in ISO 15189:2022 but only 7 in the 2012 version!

Where do references to risk appear?

- Laboratory director responsibilities
- Risk management
- Facility controls
- Equipment calibration
- Primary sample collection
- Patient consent
- Internal quality control
- Special considerations for results
- Reporting of results
- Nonconforming work
- Control of data and information management
- Continuity and emergency preparedness planning
- Management system requirements
- Actions to address risks and opportunities
- Improvement
- Nonconformities - corrective actions
- Internal audits
- Review input

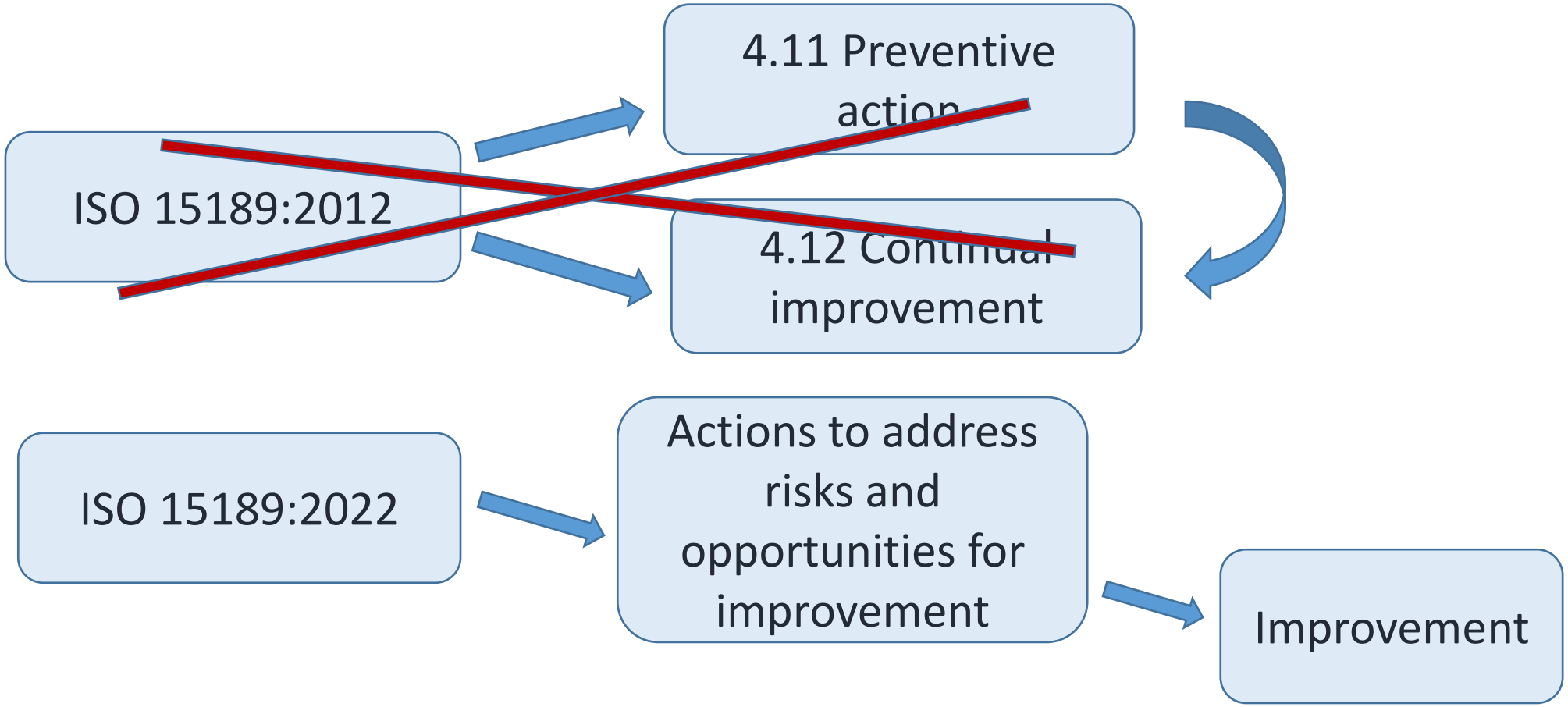

Internal Quality Control
External Quality Assessment
Nonconformities
Complaints
Evaluation
Internal Audits
Quality Indicators
Opportunities
Risks
Review Inputs
Management Review
Review Output
Effectiveness, improvement of activities and services to the patient, resources, need for change

Improvement

The laboratory shall

- seek feedback from patients, user and personnel, to be analysed and used for improvement
- maintain relevant records including the actions taken
- communicate to personnel on actions taken arising from their feedback

No reference to preventive actions . But…



Equipment calibration

The requirements are almost the same, with the addition of the risk issue…

“handling of situations when calibration was out of control, to minimise risk to service operation and to patients”

Metrological traceability of measurement results

Requirements are more detailed; reference is made to some additional supporting standards, namely ISO 17511, ISO 17034 and ISO 15194.

Metrological traceability of measurement results

The laboratory shall

a) establish and maintain metrological traceability via an unbroken chain of calibrations; each calibration contributes to the measurement uncertainty (MU) and is linked to an appropriate reference

➔ *Manufacturer's examination system without modification*

b) ensure that measurement results are traceable to the highest possible level of traceability and to the International System of Units (SI)

Traceability is documented by…

➔ *Competent calibration laboratory*

Note 1: Fulfilment of ISO/IEC 17025 - accredited (including the particular task in its scope – see also ILAC P 10) OR

➔ *Certified values of CRM - Competent producer with stated traceability to SI*

Note 2: RM producers fulfilling ISO 17034

Note 3*:* CRM fulfilling ISO 15194

In case this task is not possible to be met…

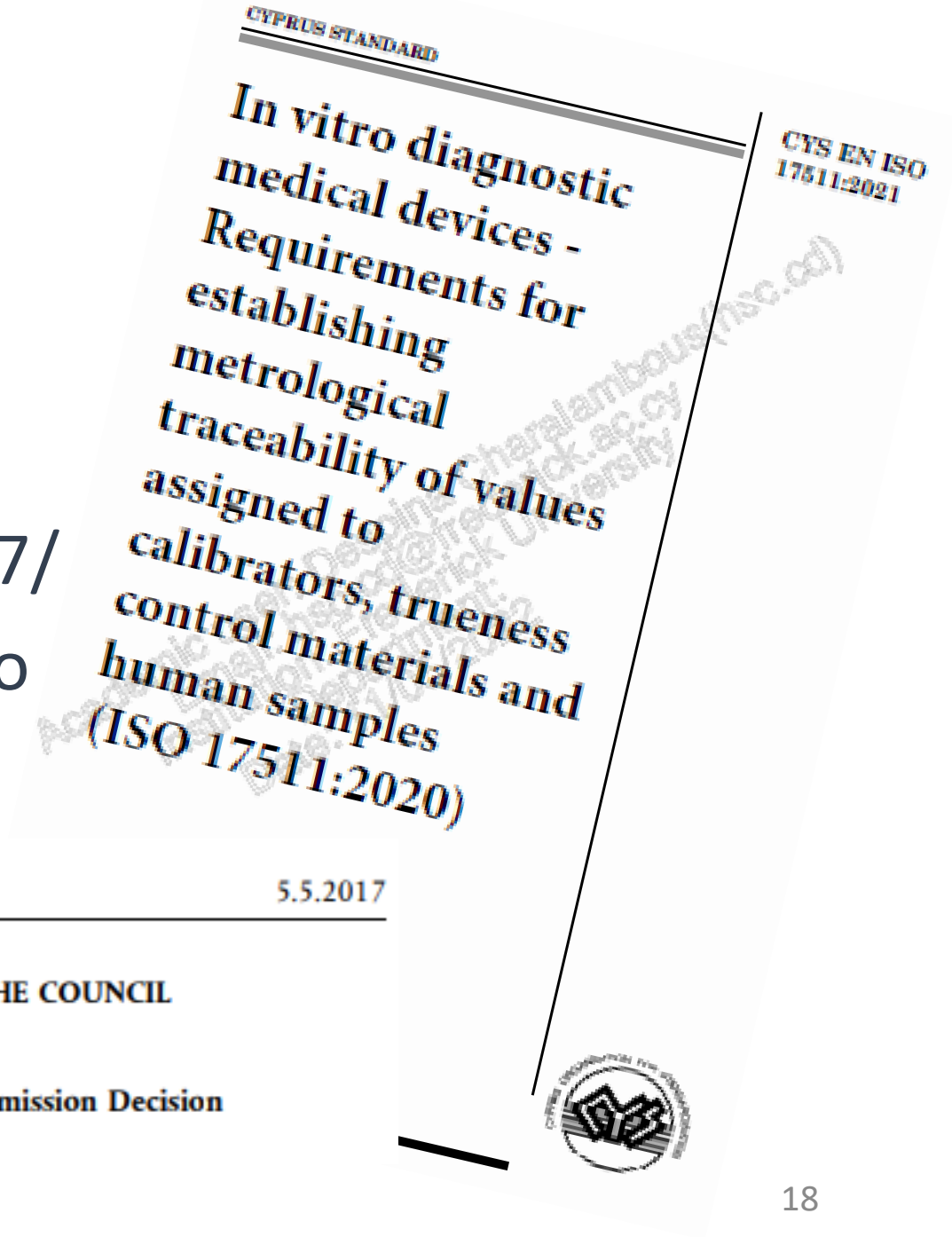
the laboratory shall use other means; among them…

- results of reference measurement procedures, specified methods or consensus standards
- measurement of calibrator by another procedure

Note: see ISO 17511 for further information to deal with compromises

This standard provides…

a voluntary means of conforming to the General Safety and Performance Requirements of Regulation (EU) 2017/746 of 5 April 2017 concerning in vitro diagnostic medical devices.


CYPRUS STANDARD

In vitro diagnostic medical devices - Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples (ISO 17511:2020)

CYS EN ISO 17511:2021

L 117/176 EN Official Journal of the European Union 5.5.2017

REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

Examination processes

Requirements are set in a more systematic way.

Selection of examination methods validated for the intended use

Preferred methods: specified in the instructions of in vitro

diagnostic medical devices OR published in textbooks/peer reviewed texts

OR journals OR standards/guidelines OR regulations

- Performance specifications shall relate to the intended use of the examination and its impact on patient care
- All documentation shall be kept up to date and available to personnel
- Established procedures shall be followed - identity of persons recorded
- Authorized personnel shall periodically evaluate the examination methods- are they clinically appropriate?

Verification OR validation of examination methods?

It depends!

Verification of validated methods…

- Can the laboratory properly perform examination methods BEFORE put into use - achieve the required performance as specified by the manufacturer or method relevant to the intended use?
- Sufficient extent to ensure validity
- Review by authorized personnel
- Repeat on each revision
- Retain appropriate records (performance, results, statement)

OR

Validation of methods…

- Laboratory designed/developed
- Outside intended scope (instructions, range, use of third party reagents)
- Modified
- Validation extensive as necessary ➔ validity of results
- Review by authorized personnel
- Review of the clinical impact in case of proposed changes
- Retain records (procedure, requirements, performance, results, statement)

Measurement uncertainty

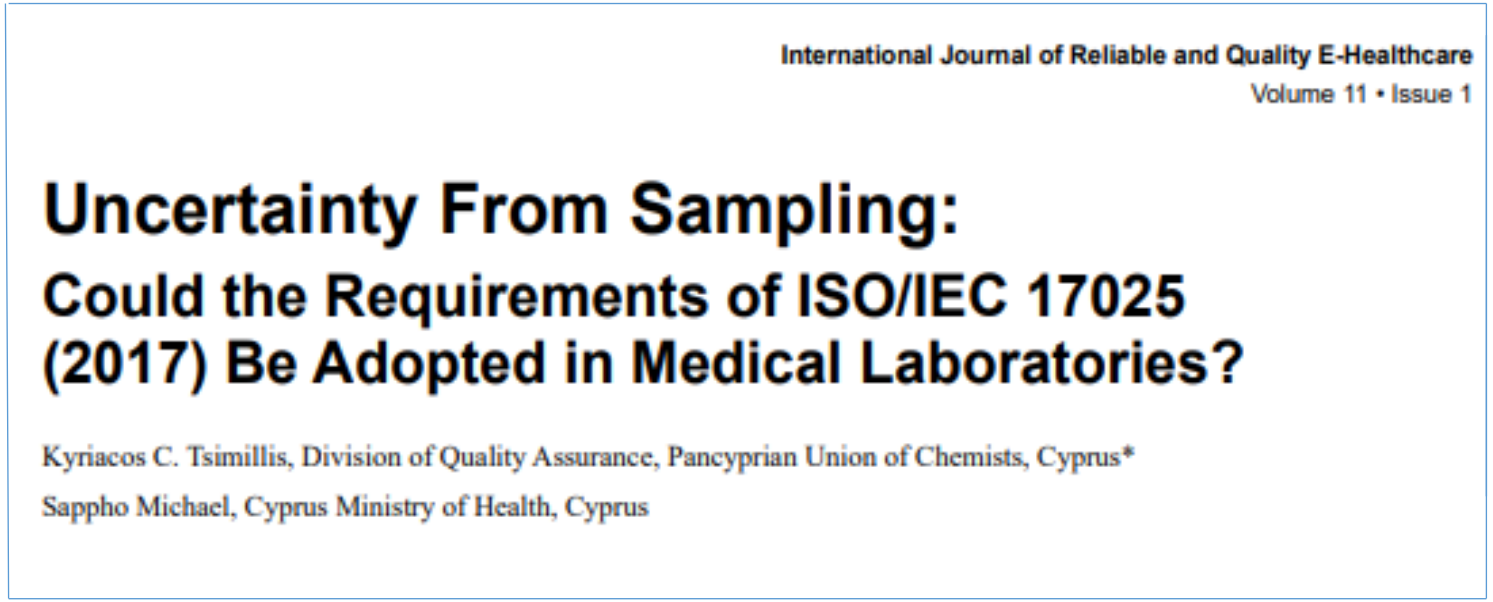
Main requirements remain the same

- Although MU is not included in the report of results, it shall be evaluated and maintained and be made available to the users on request (see ISO/TS 20914)
- MU evaluations shall be regularly reviewed
- Where and if examination procedures are excluded from MU, the rationale shall be documented
- Other sources of MU e.g. biological variation shall be taken into account following relevant inquiries
- For qualitative results, evaluation of MU is still required using positive or negative samples
- MU should be considered in verification and validation of a method.

Great emphasis is given

to sampling and the pre-examination process with reference to supporting standards e.g. ISO 20658. Detailed requirements are set for all activities included in this process. However…

Contrary to ISO/IEC 17025, the Standard makes no reference to uncertainty arising from sampling; this seems to be related to inherent difficulties in most cases for such an evaluation.


International Journal of Reliable and Quality E-Healthcare
Volume 11 • Issue 1

Uncertainty From Sampling:
Could the Requirements of ISO/IEC 17025 (2017) Be Adopted in Medical Laboratories?

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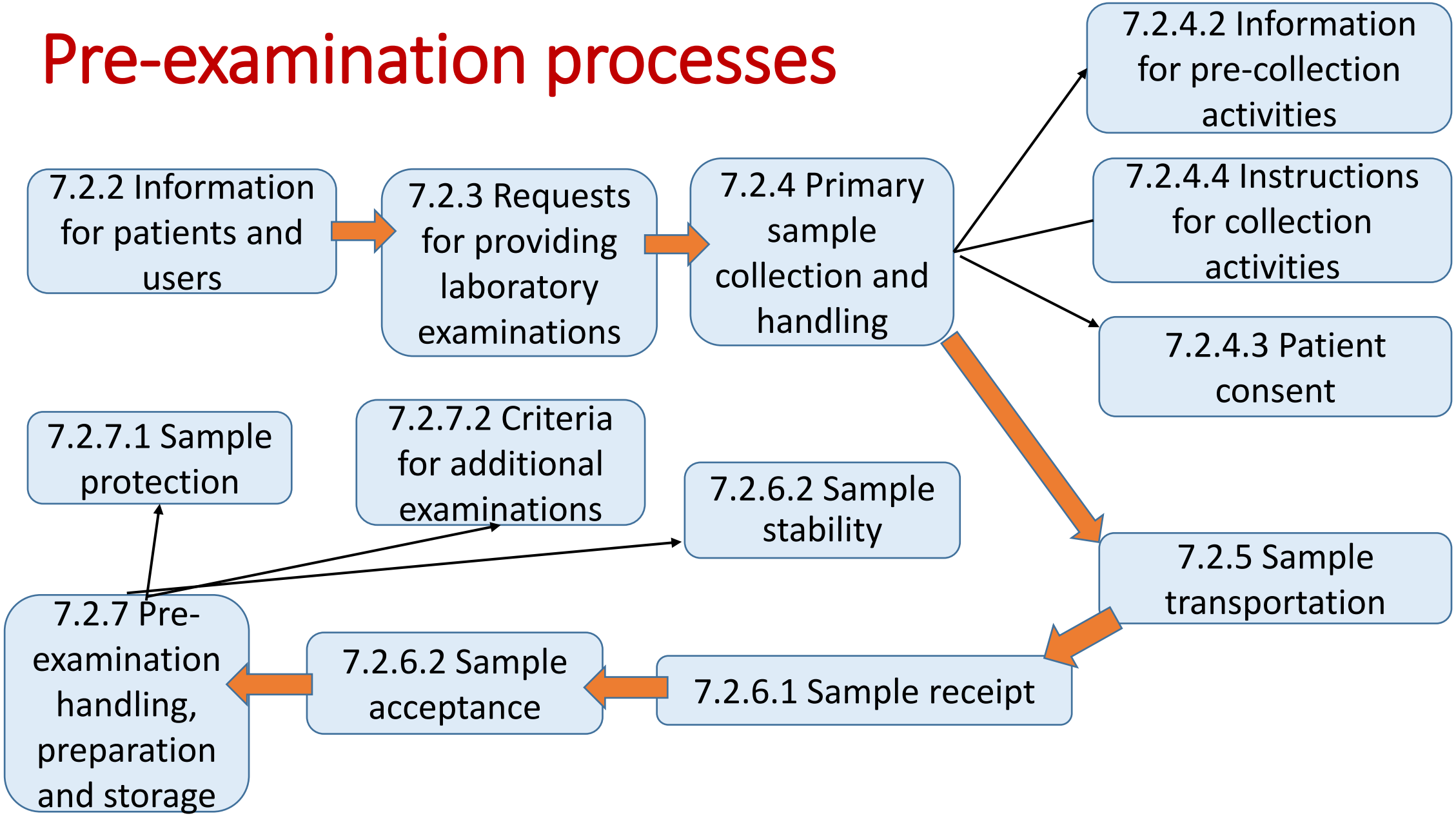
Sappho Michael, Cyprus Ministry of Health, Cyprus

Pre-examination processes



According to ISO/TS 20914…

MU only considers uncertainties arising from sources within the technical bounds of a measuring system and assumes that uncertainties due to pre- and post-analytical steps are minimised by standardising these processes.

Following a discussion in EA LC Healthcare…

Accreditation of a sampling as a stand-alone-activity? ISO/IEC 17025 or ISO/IEC 17020.

Internal quality control (IQC)

The laboratory shall have an IQC procedure to monitor the ongoing validity of the results, according to specified criteria

- The intended clinical application of the examination should be considered
- The procedure should allow for the detection of either lot-to-lot reagent or calibrator variation or both
- Third-party IQC material? It should be considered as an alternative to, or in addition to control material supplied by the reagent/ instrument manufacturer

Internal quality control (2)

How to select IQC material? To be fit for purpose!

What does this mean?

- Stability with regard to properties of interest
- Matrix as close as possible
- Reaction to the examination method as close as possible to patient sample
- Concentration levels at/near the clinical decision limits and, when possible, covering the measurement range

If an appropriate IQC is not available? Other methods…

Internal quality control (3)

Other methods may include…

- Trend analysis of patient results
- Comparison of results for patient samples on a specified schedule to results for patient samples examined by an alternative method
- Retesting of retained samples

Internal quality control (4)

More requirements…

- The frequency shall be decided based on the stability and robustness of the examination method and the risk of harm to the patient
- Data shall be recorded
- IQC data shall be reviewed with defined acceptability criteria at regular intervals
- No release of results in the event that IQC fails the criteria; the results are rejected and patient samples are re-examined after correction
- The results after the last successful IQC shall be evaluated

In medical laboratories…

all necessary equipment and materials (reagents, kits, controls and calibrators) are usually provided by the same supplier; this means that we have a “closed” system which needs to be monitored by an external source. Therefore the need for an external quality assessment is imperative.

As a result, the frequency of participation is much higher in the case of medical laboratories compared to analytical ones.

External quality assessment (EQA)

The laboratory shall monitor its performance by comparison with other laboratories. To this end…

- A procedure is required for the participation in EQA (available?)
- The personnel who routinely perform examination procedures shall be involved
- The EQA programmes shall, to the extent possible,
  - fit to all examination processes
  - mimic patient samples
  - fulfil ISO/IEC 17043 requirements.

External quality assessment (2)

- What about the target value? This is independently set by a reference method OR by overall consensus data OR by method peer group consensus data OR by a panel of experts
- What happens if there is no available/suitable scheme? The laboratory shall justify it and use alternative methodology, i.e. samples exchange with other laboratories, interlaboratory comparisons using IQC materials and other alternatives
- EQA data to be reviewed at regular intervals
- EQA results falling outside acceptability criteria ➔ corrective action
- In case the impact is clinically significant ➔ review of patient results and the need for amendment shall be considered.

Comparability of examination results

- A procedure shall be specified for establishing the comparability of results for patient samples when different methods or equipment or both are used for an examination and/or the examination is performed at different sites
- Relevant results shall be recorded
- Comparability of results shall periodically be reviewed
- Any differences and their impact shall be evaluated and acted upon
- The laboratory shall inform users of any clinically significant differences

Internal audits…

shall be conducted at planned intervals to ensure that the Management System (MS) conforms both to the laboratory's and the Standard's requirements and is effectively implemented and maintained; this needs a programme to be planned, established, implemented and maintained.
ISO 19011 provides guidance.

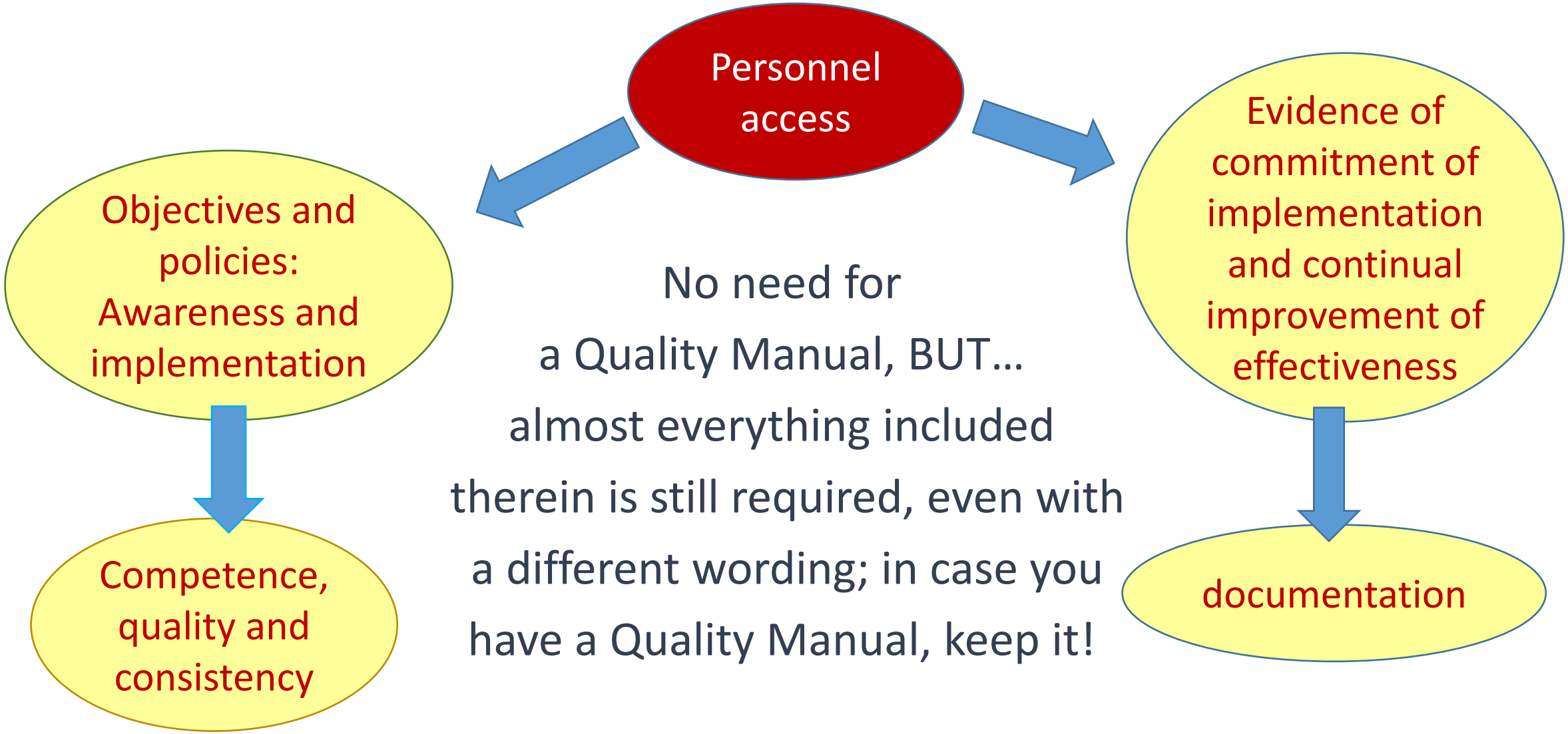
Priority shall be given to risk to patients from laboratory activities! Furthermore…

Internal audits (2)

The audit plan shall include:

- A schedule considering identified risks, outcome of both external and internal audits, occurrence of nonconformities, incidents and complaints as well as changes.
- Specified audit objectives, criteria and scope
- Selection of trained, authorized and independent *("whenever resources permit")* auditors
- Objectivity and impartiality to be ensured
- Results to be reported to relevant personnel
- Implementation of corrective actions without delay
- Retention of records

MS documentation



No need for
a Quality Manual, BUT…
almost everything included
therein is still required, even with
a different wording; in case you
have a Quality Manual, keep it!

Flexibility

Quality Management System e.g. in line with ISO 9001?
This means fulfilment of 4-7 and 8.2 -8.9

The correlation of the relevant sub-clauses (titles) does not reflect the difference in their content

However, a laboratory even certified against ISO 9001, **does not** necessarily address technical competence requirements of ISO 15189; similarly, ISO 9001 audits **could not** substitute ISO 15189 assessments

Reservation!

This issue needs to be considered in particular in the case of laboratories operating in hospital which are certified!

Despite the differences at first glance…

in practice, these are not too many or difficult to address;

the changes refer mostly to the philosophy of the document.

A transition period of three years, as is usually the practice, is considered to be adequate for both laboratories and accreditation bodies to shift smoothly to the new edition, addressing all new or adjusted requirements.

Thank you for your attention and your questions!