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ATLAS Project
ISO 15189 Accreditation Support Course

Management systems specific to molecular-genetic tests

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B.S., MT from Kitasato University

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Operation of ISO 15189

- All requirements in this international standard are versatile, and the operation method differs depending on each organization.
- This international standard is not intended for standardizing the structure or documentation of various quality management systems (QMS).
- The requirements for QMS specified in this international standard do not complement all requirements for clinical laboratories.

Classification of molecular-genetic tests

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1. Pathogen nucleic acid tests for detecting pathogens:

   Testing to detect and analyze the nucleic acid (DNA or RNA) of exogenous pathogens (viruses, bacteria, etc.) that cause infectious diseases in humans.

2. Molecular tests for humans:

   ① Molecular tests for detecting somatic gene alterations: molecular testing to detect transient localized alterations in the genetic information induced in response to disease development, e.g., tests used to detect structural abnormalities in genes unique to cancer cells and gene expression analysis.

   ② Molecular tests for detecting germline alterations: testing to identify genetic information specific to an individual that can be passed from generation to generation that can result in the development of monogenic diseases and multifactorial diseases and impact drug metabolism and side effects. These tests can also be used for individual identification.

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Quality assurance of molecular-genetic tests

- In recent years, the development and clinical application of molecular-genetic tests based on new technologies have rapidly progressed. Many reagents for molecular-genetic tests are not laboratory-approved *in vitro* diagnostic devices (IVDs) but are often developed independently in the laboratory (laboratory-developed tests: LDT).
- In analyses using proprietary reagents, the data vary among the examination facilities because of differences in the examination methods, equipment, and examination processes.
- The utilization of these new analysis technologies is dependent on the quality and standardization of examinations and on the development of QMSs in facilities in line with patient needs and technological advances.

Scope

- This International Standard specifies the requirements for quality and competence in medical laboratories.
- This International Standard can be used by medical laboratories to develop their quality management systems and assess their own competence. It can also be used to confirm or recognize the competence of medical laboratories by customers, regulatory authorities, and accreditation bodies.
- International, national, or regional regulations or requirements may also apply to specific topics covered in this International Standard.

Scope

- If there are requirements that do not apply to the organization, it is necessary to justify why it should not affect the organization's ability or responsibility to ensure the conformity of inspections and services.
- 4.2.2.2 b) The requirement “Description of the scope of application of the quality management system” is also relevant.
- It is necessary to clarify "business to be managed" and "business not managed". Particularly, it is necessary to decide on outsourced work.
- Based on the nature of the product/service, it can be interpreted that procedures (clauses) for which the facility is not equipped need not be carried out. It is necessary to define the "scope of business to be managed" in a document. Here, the "target examination/service" in must be understood by outsiders.
- If there are tests that "do not exist in your facility" among the requirements of International Standards, it is necessary to explain the reason in a document.

Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

- *ISO/IEC 17000, Conformity assessment — Vocabulary and general principles*
- *ISO/IEC 17025:2005, General requirements for the competence of testing and calibration laboratories*
- *ISO/IEC Guide 2, Standardization and related activities — General vocabulary*
- *ISO/IEC Guide 99, International vocabulary of metrology — Basic and general concepts and associated terms (VIM)*

Guidelines for molecular-genetic tests issued by JCCLS

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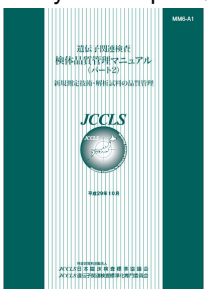
Japanese Version of Best Practice Guidelines for Molecular-genetic Tests Commentary Version

Molecular-genetic Tests Specimen Quality Control Manual (approval document)

Molecular-genetic Tests Specimen Quality Control Manual (Part 2) New Measurement Technology/ Analysis Sample Quality Control Approval Document



ISO 15189 Guidance Document for Molecular-genetic Tests

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Process of Specimen Examination

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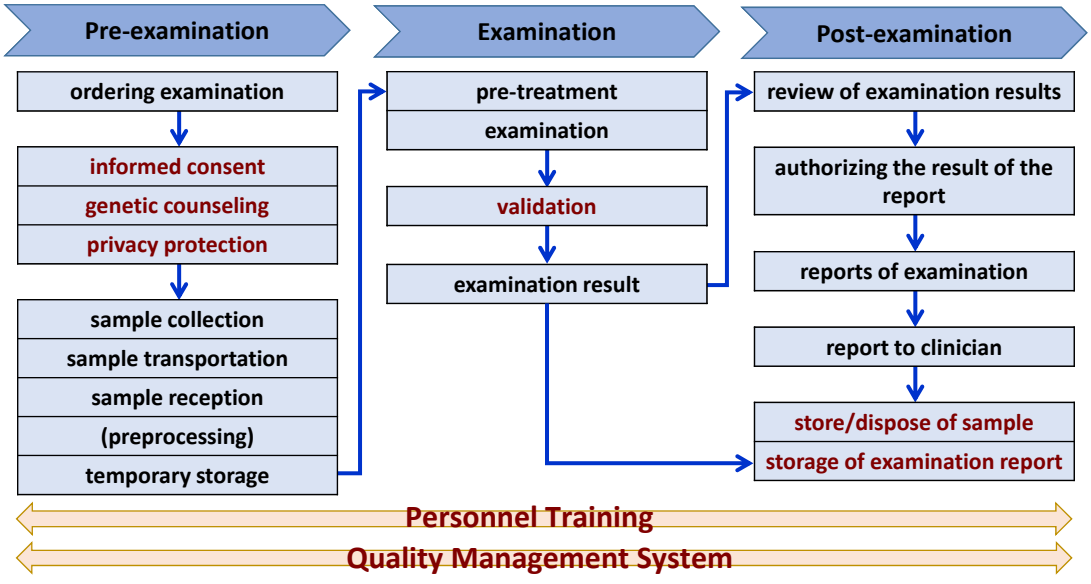

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Requirement number and number of nonconformities

(June–Nov. 2020)

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Management requirements

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- 4.2 Quality management system
- 4.3 Document control
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- 4.15 Management review

3. Management requirements in ISO 15189

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4.1.1.3 Ethical conduct

Laboratory management shall have arrangements in place to ensure the following:
e) confidentiality of information is maintained

- Genetic testing must be performed in a scientifically and technically correct manner while considering legal and ethical aspects.
- However, the laboratory should provide information only to relevant parties such as medical institutions or registered clinical laboratories requesting the analysis in advance about the conditions for submitting gene sequence data and reliability of additional information, but also refer to international, national or regional regulations or requirements for the preparation of standard operating procedure and information security measures , if necessary.

4.1.1.4 Laboratory director

The laboratory director may delegate selected duties and/or responsibilities to qualified personnel; however, the laboratory director shall have the ultimate responsibility for the overall operations and administration of the laboratory.

The laboratory director shall have the necessary competence, authority, and resources in order to fulfil the requirements of this international standard.

4.1.2.1 Management commitment

Laboratory management shall provide evidence of its commitment to the development and implementation of the quality management system and continually improve its effectiveness by:

a) communicating to the laboratory personnel the importance of meeting the needs and requirements of users as well as regulatory and accreditation requirements;

b) establishing the quality policy

c) ensuring that quality objectives and planning are established

d) defining responsibilities, authorities and interrelationships of all personnel

e) establishing communication processes

f) appointing a quality manager, however named

g) conducting management reviews

4.1.2.3 Quality policy

Laboratory management shall define the intent of its quality management system in a quality policy. Laboratory management shall ensure that the quality policy:

a) appropriately matches the purpose of the organization;

b) includes a commitment to good professional practice, examinations that are fit for intended use and complies with the requirements of this International Standard, and aims to continually improve the quality of laboratory services;

c) provides a framework for establishing and reviewing quality objectives;

d) is communicated and understood within the organization;

e) is reviewed for continuing suitability.

Appointment of technical managements

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Laboratory management shall ensure that responsibilities, authorities, and interrelationships are defined, documented, and communicated within the laboratory organization.
This shall include the appointment of the person(s) responsible for each laboratory function and appointment of deputies for key managerial and ***technical personnel.***

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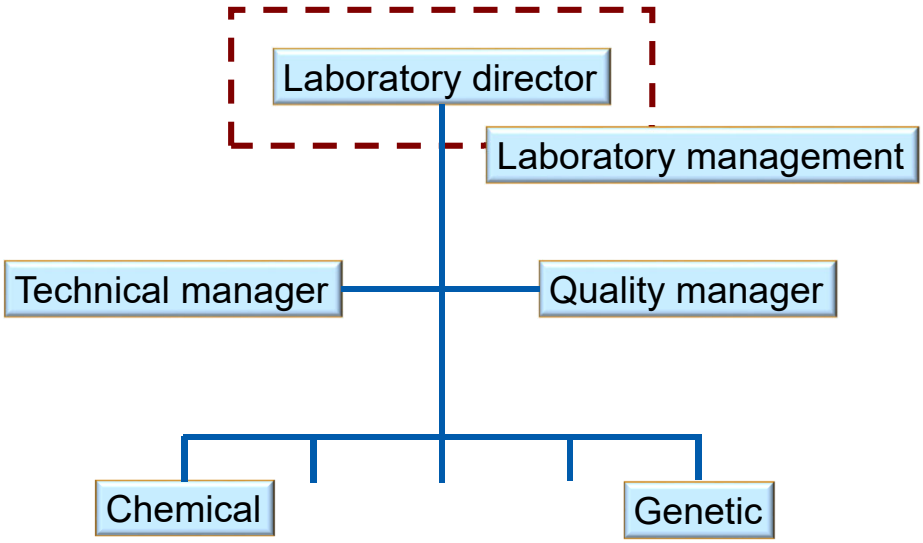
Quality policy and quality objectives

4.1.2.7 Quality manager

Laboratory management shall appoint a quality manager who shall have, irrespective of other responsibilities, delegated responsibility and authority that include:

- Appointment of an individual responsible for ensuring quality. It should be noted that the law that partially amends the medical regulations, allows concurrent appointment of a person in charge of ensuring the quality of overall clinical laboratory tests. With respect to qualifications, expertise in all medical laboratory quality controls and clinical tests including molecular-genetic tests testing, appropriate experience, and qualities is required.

A representative functional organization chart



3. Management requirements in ISO 15189

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4.2 Quality management system

4.2.2.1 General
The documentation of quality management system shall include:
e) copies of applicable regulations, standards, and other normative documents.

- As the workflow of the new NGS-based clinical tests is much more complex than that of traditional Sanger sequencing-based tests, new regulatory standards are being developed for laboratories offering these tests.

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4.3 Document control

The laboratory shall manage the filing of documents required by the quality management system and shall ensure that the unintended use of any obsolete document is prevented.

- The laboratory shall create standard operating procedures (SOPs), strive to standardize operations, and perform all operations in accordance with the standardized SOPs. In addition, the laboratory shall maintain operation records and/or logs, in addition to having a history of non-conformities, errors, and corrections. The laboratory should conduct continuous improvements. The laboratory shall create documents and ensure that they are in the correct formats. Additionally, laboratories should review these documents regularly and manage and store them appropriately.

4.3 Document control

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The laboratory shall have a documented procedure for ensuring that the following conditions are met.

a) All documents, including those maintained in a computerized system, issued as part of the quality management system are reviewed and approved by authorized personnel before issue.

b) Ensure that all documents include:

- *a title;*
- *a unique identifier on each page;*
- *the date of the current edition and/or edition number;*
- *page number to total number of pages (e.g., “Page 1 of 5,” “Page 2 of 5”);*
- *identity of the person with the authority to issue the document.*

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Document control flow

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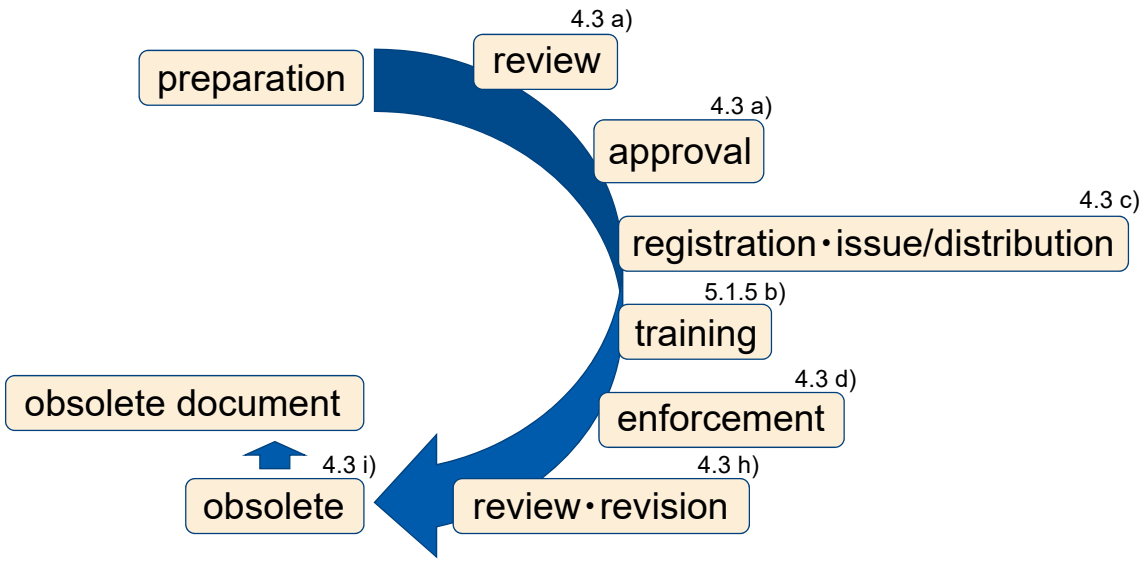

4.3 Document control

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Precautions to be taken when records are documented and revised:

【Edition Traceability (Version etc.)】

- The laboratory should ensure that specific version(s) of the bioinformatics pipeline used to generate NGS data files are traceable for each patient report.

【Monitoring of Upgrades】

- The laboratory should have a policy for monitoring, implementing, and documenting upgrades to instruments, sequencing chemistries, and reagents or kits used to generate NGS data.
- This policy should also address the methods used to monitor upgrades and record the specific time when a relevant upgrade(s) will be implemented and validated before productive clinical use.

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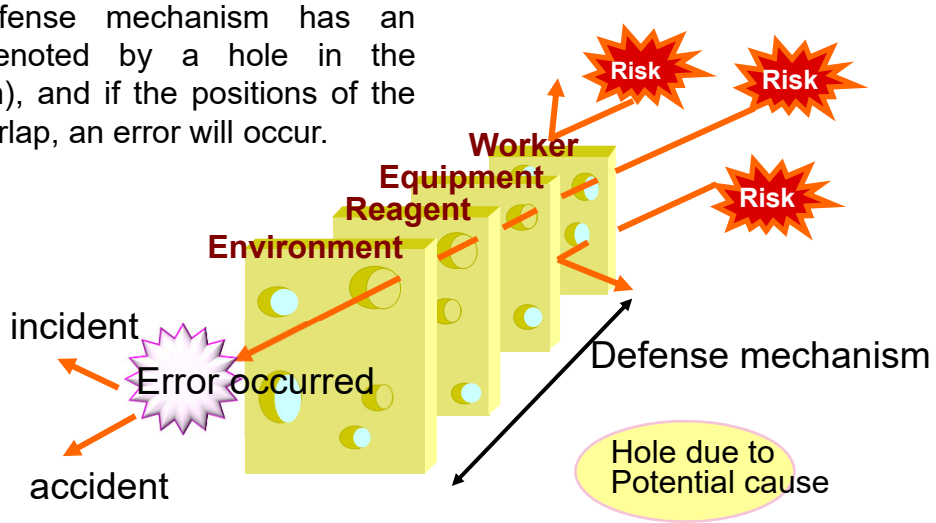
Swiss cheese model

Each defense mechanism has an issue (denoted by a hole in the illustration), and if the positions of the holes overlap, an error will occur.



Nonconforming examinations or activities can be identified in many different ways

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- clinician complaints
- staff comments
- laboratory management reviews
- internal and external audits
- instrument calibrations
- checking of consumable materials
- reporting and certificate checking
- quality control chart
- internal quality control indications
- interlaboratory comparisons

4.10 Corrective action

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The laboratory shall take corrective action to eliminate the cause(s) of nonconformities. Corrective actions shall appropriately target the nonconformities encountered. The laboratory shall have a documented procedure for:

- Addressing common problems that arise during testing. “Problems” include events that can affect the test result or its clinical use as well as nonconformities with the laboratory’s own policies and procedures. Documentation includes the review of the effectiveness of the corrective actions taken and the revision of policies and procedures intended to prevent recurrence.

Problems with corrective action

Corrective action refers to the action to eliminate the root cause of the detected nonconformity.

These are the common problems requiring corrective action:

1. The event and cause have not been distinguished
2. The true cause has not been determined
3. The cause is considered as a person's responsibility
4. The efficacy of the corrective action has not been confirmed
5. Past cases have not been analyzed

Examples of corrective actions to find the root cause

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Nonconformity: Mr. A's work procedure deviated from the SOP

↓

Primary cause: Mr. A did not follow the SOP

↓

Secondary cause: Mr. A did not know about the change in the SOP

↓

Third cause: He didn't know because he was absent from the SOP workshop

↓

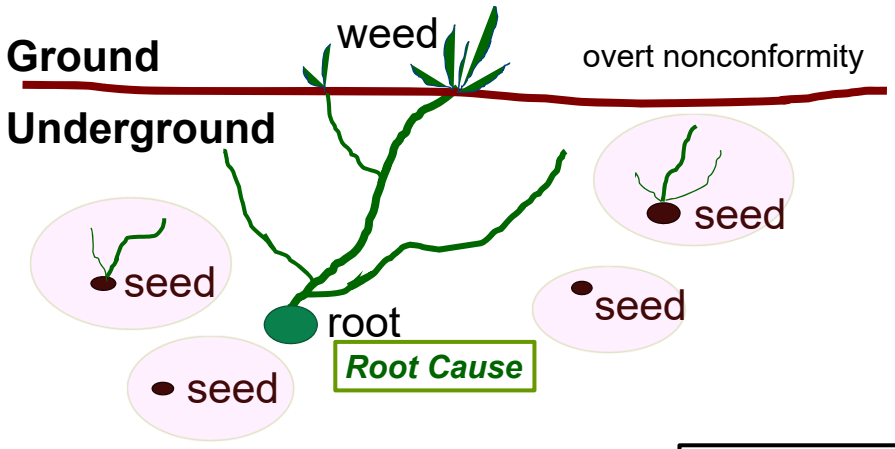
Fourth cause: The information was not provided to the absentees

↓

Root cause: There was no mechanism to follow absentees

Specific measures can be formulated

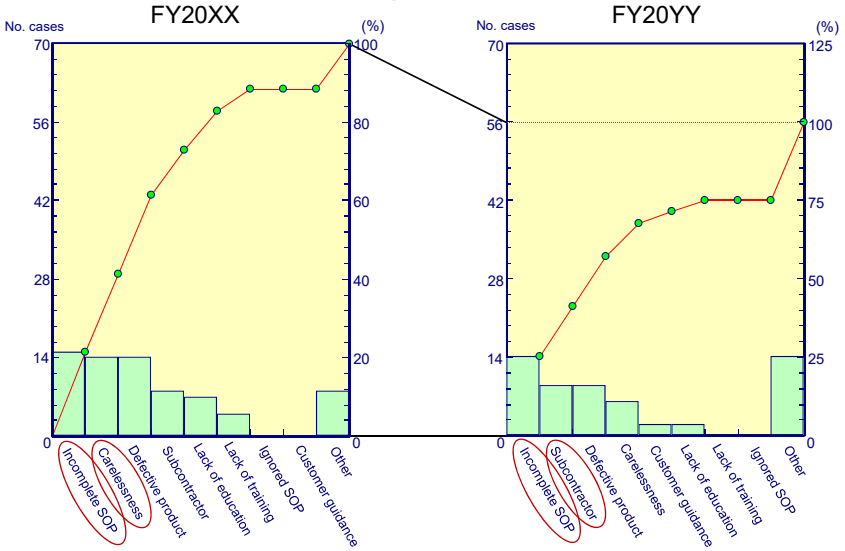
Root Cause Analysis



potential nonconformity = ***Preventive Action***

Example of root cause trend analysis

(Pareto chart from the reporting of complaints to their resolution)



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4.13 Control records

The laboratory shall have a documented procedure for identification, collection, indexing, access, storage, maintenance, amendment, and safe disposal of quality and technical records.

【Laboratory Records】

Methods, instrument(s), and reagents used for processing and analyzing sample (specimen) (or batch of samples) must be identifiable and traceable in the laboratory's records.

【Data Storage】

The laboratory should have a policy regarding the storage of input, intermediate, and final data files generated by the bioinformatics pipeline. Legal liability concerns regarding certain types of genetic examination procedures may require the retention of certain records for much longer periods than that required for other types of records.

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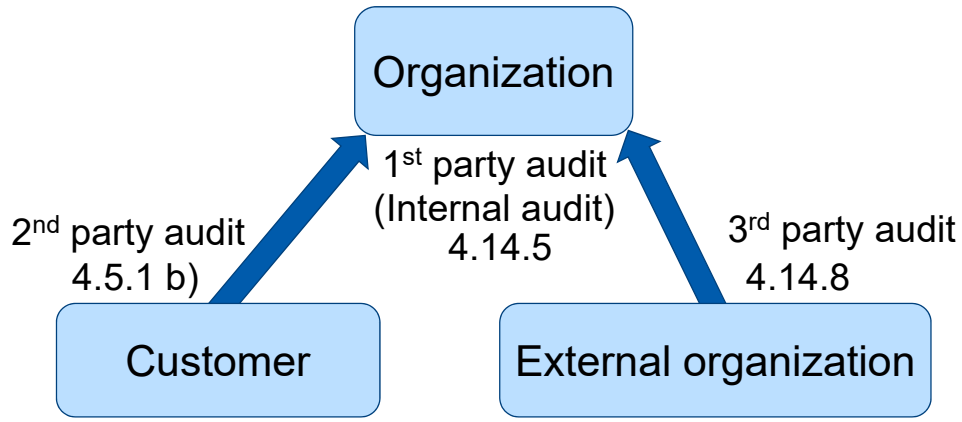
Type of audit



Flow of internal audit activities

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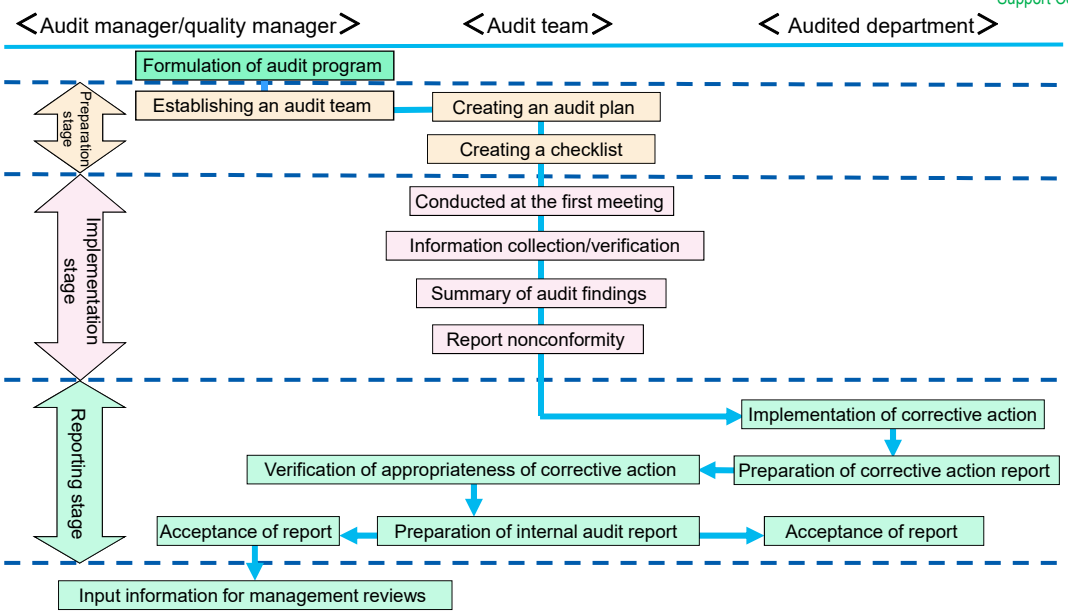

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4.15 Management review (1/4)

Laboratory management shall review the quality management system at planned intervals to ensure its continuing suitability, adequacy, and effectiveness, and support of patient care.

The output from the management review shall be incorporated into a record that documents any decisions made and actions taken during management review related to:

a) improvement of the effectiveness of the quality management system and its processes;

b) improvement of services;

c) resource needs.

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Process-based QMS model

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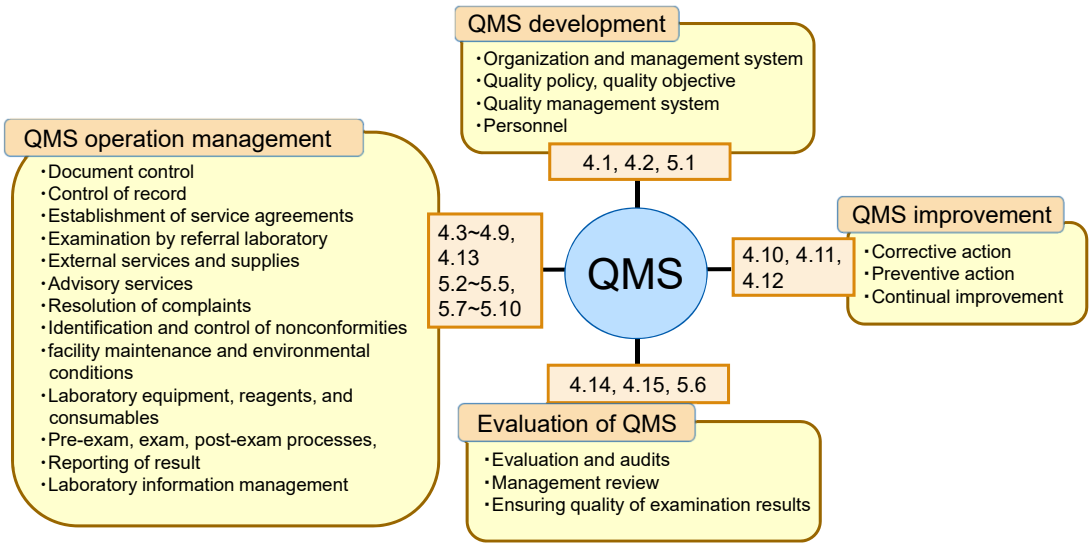

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Process-based QMS model

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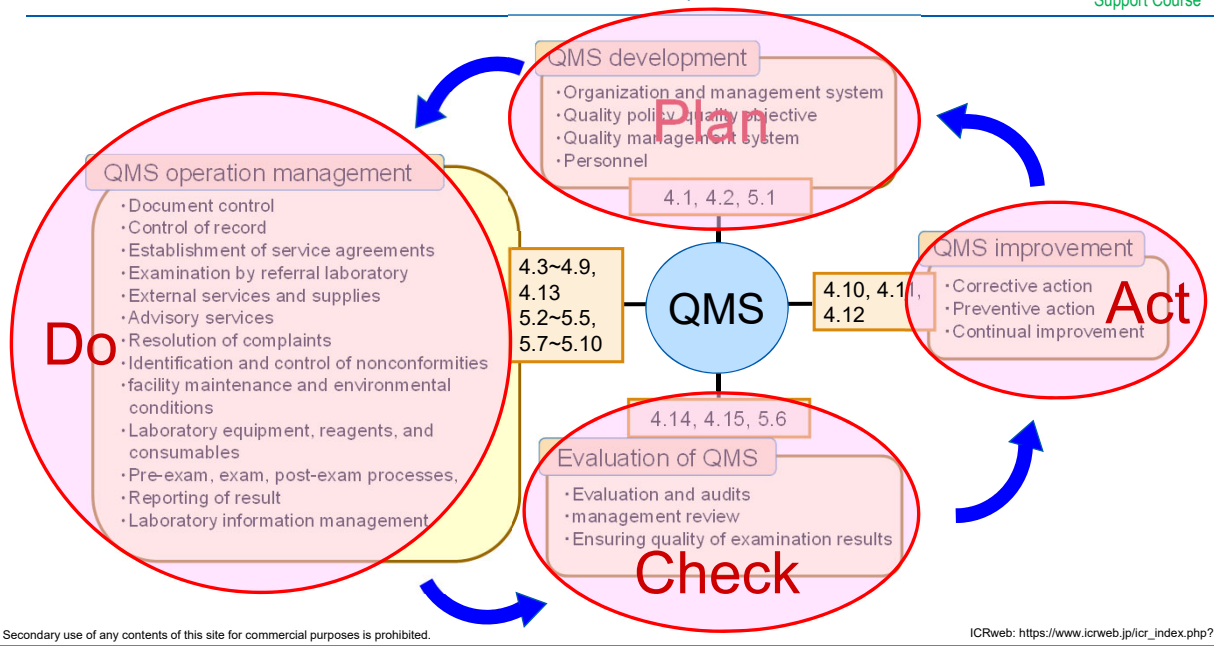

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Quality management principles

This document introduces seven quality management principles (QMPs).

ISO 9000, ISO 9001, and related ISO quality management standards are based on these seven QMPs.

1. Customer focus
2. Leadership
3. Engagement of people
4. Process approach
5. Improvement
6. Evidence-based decision-making
7. Relationship management

24th ISO/TC 212 Plenary Meeting at Mexico City

November 2019

"We hope that you understand QMS more than ever through this training."