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Technical requirements specific to molecular-genetic tests (Part-1)

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Japan bio Measurement & Analysis Consortium (JMAC)
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Before joining establishment of JMAC:
Research Scientist at Toshiba Corporation 1986–1999
Bioinformatics business division in Hitachi Ltd. 1999–2005
CEO of Canaledge 2003–2005
Director of Medibic Group 2006–2009
Director of Genetic Lab 2009–2013
President and CEO of Bio-business solutions (present)

Education
Ph.D. from Chiba University in 1993
Post Doctoral Associate, Universität des Saarlandes, Germany 1994–1996

Specialty and Research Field of Interest
Molecular Biology and Bioinformatics

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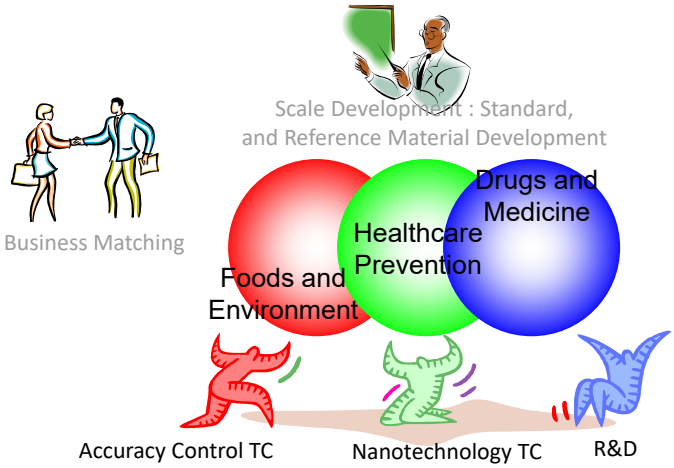
ISO-Related Activities

- ISO-RELATED ASSIGNMENT
  - ISO/TC 34/SC 16/WG 9 Secretary
  - ISO/TC 34 Expert (WG 14, SC 16, SC 16/WG 8, 10)
  - ISO/TC 212 Expert (WG 1, 4)
  - ISO/TC 229 Expert (WG 1, 5)
  - ISO/TC 276 Expert (WG 2, 3, 4, 5)
  - ISO/TC 34/SC 9 Liaison Representative (TC 276/WG 5)
  - ISO/TC 272 Liaison Representative (TC 276)
  - CEN/TC 275/WG 11 Observer
- ISO-RELATED QUALIFICATION
  - IRCA QMS Lead Auditor Certification No. 601574, May 2014
  - IRCA FSMS Provisional Auditor Certification (Same No. as QMS), July 2017
  - JAB Testing Laboratory Technical Assessor (ISO/IEC 17025), April 2016
  - JAB Clinical Laboratory Senior Assessor (ISO 15189) April 2017
  - JRCA, Standard Development Expert RCES, No. SE00047, Japan, January 2018

Japan bio-Measurement & Analysis Consortium

Purpose of foundation: Market Creation and Acceleration of Bio-industry
- Activity leading to expansion of the health care industry -

2007-10-19 Private Organization
2008-10-24 NPO
2018-10-29 Name Change



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Biobank considerations

Personnel requirements for biobank

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Overview of technical requirements in ISO 15189

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Overview of technical requirements in ISO 15189

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- Resources (5.1–5.3)
  - Personnel, accommodation and environmental conditions, equipment, reagents, and consumables.
- Pre-examination processes (5.4)
  - Information for patients and users, request form, primary sample, instructions for collection, sample transportation, reception, pre-examination handling, preparation and storage.
- Examination process and ensuring the quality of the examination results (5.5, 5.6)
  - Selection, verification, validation of procedures, measurement uncertainty (MU), biological reference intervals or clinical decision values, standard operating procedure (SOP), quality control (QC) materials and data, interlaboratory comparisons, comparability of results.
- Post-examination processes (5.7)
  - Review of results and storage, retention and disposal of clinical samples
- Reporting and release of results (5.8, 5.9)
- Laboratory information management (5.10)

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5.2 Laboratory design and facility: How to prevent contamination

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5.2 Laboratory design and facility: How to prevent contamination

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5.2.1 General

The laboratory shall:

have space allocated for performing work
- be designed to ensure the
  - quality, safety and efficacy of the service provided to the users
  - health and safety of laboratory personnel, patients, and visitors.

evaluate and determine the sufficiency and adequacy
- of the space allocated for performing work.

It is necessary to establish a safety management plan for pathogens based on biosafety and strive to prevent unintentional exposure or leakage of pathogens and toxins (see 5.2.6).

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5.2 Laboratory design and facility: How to prevent contamination

5.2.2 Laboratory and office facilities

The laboratory and associated office facilities shall control:

a) Access to areas affecting the quality of examinations.
--- safety, confidentiality, quality, and prevailing practice.

Depending on the operation to be conducted, it may be necessary to restrict access to specific areas of the laboratory. If restricted access is in effect, personnel should be informed of the following:

- Purpose of using a specific area
- Operational restrictions in the area
- Reason for the restrictions
- Actions taken when such restrictions are violated

The laboratory has established a safety management plan for pathogens based on the concept of biosafety, etc., and made efforts to prevent unintended exposure or leakage of pathogens and toxins.

5.2 Laboratory design and facility: How to prevent contamination

5.2.2 Laboratory and office facilities

The laboratory and associated office facilities shall control:

b) Access to medical information, patient samples, and laboratory resources

To prevent theft or loss of personal data, the laboratory shall take the following physical security management actions.

Entrance/exit (room) management, preventive actions against theft (for example, filming with a camera/video), and physical protection such as fixing of equipment and/or devices, etc.

Based on the operational needs to prevent unauthorized operations, the functions given to terminals that handle personal data are restricted as follows: connection restrictions and response to device updates for devices with recording functions such as smartphones and personal computers.

5.2 Laboratory design and facility: How to prevent contamination

5.2.2 Laboratory and office facilities

The laboratory and associated office facilities shall control:

e) Safety facilities and devices, with regular verification

During UV - irradiation, UV-blocking protective glasses or protective shield glass shall be used to avoid looking directly at UV rays.

5.2 Laboratory design and facility: How to prevent contamination

5.2.6 Facility maintenance and environmental conditions

Laboratory premises: maintained in a functional and reliable condition.

Work areas: clean and well-maintained.

Environmental conditions: monitor, control, and record (when specified or when at risk of influencing the quality of the sample, results, and/or health of staff.)

Deviations from the limits of environmental conditions may be identified by monitoring the system or through quality assurance of certain analyses. The impacts of deviations from the environment may be assessed during the robustness test through validation. Emergency operating procedures shall be established as appropriate.

All temperature-controlled equipment and environmental conditions shall be checked daily.

5.2 Laboratory design and facility: How to prevent contamination

- ✓ In the biobank, there is the evidence that samples (specimens) are stored at the required temperature according to the protocol.
- ✓ In the biobank, the temperature is checked daily with a thermometer for all temperature depending on the equipment and environment.
- ✓ In the biobank, when the temperature exceeds the acceptable range, appropriate corrective action shall be taken, after which the temperature shall be checked again and recorded.
- ✓ The identity of the individual recording the temperature(s) shall be documented (recording the initials of the individual is adequate).
- ✓ Use of automated (including remote) temperature monitoring systems is acceptable, and the functionality of the system shall be documented daily.
- ✓ In the biobank, temperature-controlled storage equipment has an emergency power supply, if necessary.
- ✓ There are documented procedures that can be followed if there are deviations in the storage temperature limits.
- ✓ Alarm systems shall continue to function if the power is interrupted.
- ✓ Temperature-acceptable limits for the alarm system are established with consideration of the anticipated response time (see RM300 5.3.1.7).

5.2 Laboratory design and facility: How to prevent contamination

5.2.6 Facility maintenance and environmental conditions

Effective separation between incompatible activities

A molecular laboratory should be divided into at least two areas, a nucleic acid extraction/amplification reagent preparation area and an amplification/detection area, to avoid contamination by nucleic acid amplification products. When molecular testing equipment are fully automated, it is necessary to ensure that contamination measures are taken according to the internal structure of the equipment (see 5.2).

5.2 Laboratory design and facility: How to prevent contamination

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5.2.6 Facility maintenance and environmental conditions

Effective separation between incompatible activities

・A clean bench on which the inside area is maintained as clean should be used for preparing nucleic acid extraction/amplification reagents. The clean bench shall be used as the area for preparing amplification reagents.

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5.2 Laboratory design and facility: How to prevent contamination

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5.2.6 Facility maintenance and environmental conditions

Effective separation between incompatible activities

・Under the Law on Clinical Laboratory Technicians, etc. (before the 2018 revision), registered clinical laboratories that carry out molecular testing in the classification of clinical laboratory tests are required to have a safety cabinet as machinery and equipment for testing.

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5.2 Laboratory design and facility: How to prevent contamination

5.2.6 Facility maintenance and environmental conditions

Effective separation between incompatible activities

・ If the room cannot be divided, the nucleic acid extraction area and amplification reagent preparation area shoud be separated using a desktop biosafety cabinet with ultraviolet rays. If no hood equipped with an ultraviolet irradiation device is available, it is also effective to change the measurement location and wipe the laboratory bench top, followed by thorough pipetting with 0.5% sodium hypochlorite aqueous solution before and after use.

5.2 Laboratory design and facility: How to prevent contamination

5.2.6 Facility maintenance and environmental conditions

Effective separation between incompatible activities

・Pipettes, tips with filters, and tubes are dedicated for use in each area, and DNA is destroyed by irradiation with ultraviolet rays before and after use. It is desirable to prepare two sets of pipettes, one for reagents and one for samples.

[Note]

・Use a clean bench when preparing reagents and a biosafety cabinet when handling infectious specimens. The biosafety cabinet was removed from the revised Law on Clinical Laboratory Technicians, etc.

5.2 Laboratory design and facility: How to prevent contamination

5.2.6 Facility maintenance and environmental conditions

Effective separation between incompatible activities

- When selecting a designated area for new operation, the previous use of that area shall be considered.

5.3 Equipment and reagent management

5.3 Equipment and reagent management

5.3.1.2 Equipment acceptance testing

Equipment verification: upon installation and before use

> Equipment is capable of achieving the necessary performance

> Complies with requirements relevant to any examinations performed

・ The laboratory shall verify the specifications of the equipment and related requirements for testing. The applicable items are as follows:

・ Installation Qualification (IQ):

After installation in the location of use, it is necessary to confirm and document whether the equipment specifications are appropriate and whether the equipment is set up accurately, including its safety functions. Confirmation of installation qualification for all equipment used for testing, education, and training shall be completed (see 5.3.1.3).

5.3 Equipment and reagent management

5.3.1.2 Equipment acceptance testing

Equipment verification: upon installation and before use

> Equipment is capable of achieving the necessary performance

> Complies with requirements relevant to any examinations concerned

・ Operational Qualification (OQ), Performance Qualification (PQ):

It is necessary to confirm that the required functions and performance of the equipment and measurement system are obtained through various tests/checks.

[Note] OQ and PQ shall be conducted on a regular basis.

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5.5 Verification and validation of examination procedures

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5.5.1.1 General

Examination procedures: validated for the intended use

Operator: identity and record the persons performing activities in examination processes

Specific requirements (performance specifications)

<-> Intended use of that examination

・The laboratory shall select a measurement procedure that meet the user's needs, including sampling methods, and are suitable for the testing performed. The laboratory selects an appropriate method published as international standards, regional or national standards, publications of well-established technical institutions, relevant scientific literature, or periodicals.

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5.5 Verification and validation of examination procedures

5.5.1.2 Verification of examination procedures

- Verification:
  - > validated examination procedures used without modification
  - > before being introduced into routine use

[Note] Next-generation sequencing (NGS)-based tests approved by Pharmaceutical affairs correspond with this section.

5.5 Verification and validation of examination procedures

5.5.1.2 Verification of examination procedures

- Verification:
  - > Confirm that the performance claims for the examination procedure have been met
  - > Obtain objective evidence in the form of performance characteristics
  - > Performance claims <-> intended use of examination results

The following verification is required before reporting the testing results to the patient.

Accuracy:

・Closeness of agreement between a measured quantity value and true quantity value of a measure

・Definition in NGS is the closeness of agreement between the nucleic acid sequence derived from the assay and a reference sequence

5.5 Verification and validation of examination procedures

5.5.1.2 Verification of examination procedures

- Verification:
  - > Confirm that the performance claims for the examination procedure have been met
  - > Obtain objective evidence in the form of performance characteristics
  - > Performance claims <-> intended use of examination results

Precision:

・Closeness of agreement between indications or measured quantity values obtained from replicate measurements on the same or similar objects under specified conditions. Measurement precision is typically expressed numerically by measures of imprecision, such as standard deviation, variance, or coefficient of variation under the specified conditions of measurement.

・The definition in NGS is the closeness to which repeated sequence analyses give the same result: repeatability and reproducibility.

5.5 Verification and validation of examination procedures

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5.5.1.2 Verification of examination procedures

- Verification:
  - > Confirm that the performance claims for the examination procedure have been met
  - > Obtain objective evidence in the form of performance characteristics
  - > Performance claims <-> intended use of examination results

Reportable range:

・Definition in NGS is the genome region in which sequences of an acceptable quality are derived in the laboratory test.

Reference range:

・Definition in NGS is the range of base sequence variations detected in an unaffected population.

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5.4 Pre-examination handling, preparation and storage, collection

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5.4 Pre-examination handling, preparation and storage, collection

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5.4.2 Information for patients and users

g) Instructions for patient-collected samples

・The person responsible for sample collection is informed of how to handle and store the various collected samples (specimens).

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5.4 Pre-examination handling, preparation and storage, collection

5.4.2 Information for patients and users

i) Any requirements for patient consent

consent to disclose followings to relevant healthcare professionals

> clinical information

> family history

・Molecular testing laboratory should disclose information on the characteristic and limitations of the tests provided including analytical validity, clinical validity, and clinical utility.

・ The laboratory facilities should ensure that service users understand the latest evidence of the clinical validity and usefulness of the provided tests.

5.4 Pre-examination handling, preparation and storage, collection

5.4.2 Information for patients and users

Laboratory services

including an explanation of the clinical procedure to be performed to enable informed consent

・ The laboratory ensures that consent is obtained from the patient with sufficient explanation regarding the implementation of the test and before and after the test.

・ If necessary, medical doctors, licensed doctors of clinical geneticists, licensed doctors of clinical laboratory specialists, and personnel (pharmacists, nurses, medical technologists, etc.) with expertise in pharmacogenomics testing explain the test to the subjects (see 5.9.1 Note 1).

・ There is an explanation procedure for the subject when conducting a molecular test.

5.4 Pre-examination handling, preparation and storage, collection

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5.4.2 Information for patients and users

Laboratory services

including an explanation of the clinical procedure to be performed to enable informed consent

・Because the items to be explained to the subject differ depending on the product and content of the pharmacogenomics test, information on the characteristics of the product/test is obtained from the providing company (diagnostic drug manufacturer and registrated clinical laboratory). The same information is provided to the subject when medical institution performs tests using laboratory-developed methods.

・In the biobank, the sample provider is notified of how to share the obtained data.

・There are procedures and records of informed consent when conducting molecular tests.

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5.4 Pre-examination handling, preparation and storage, collection

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5.4.2 Information for patients and users

Laboratory services

including an explanation of the clinical procedure to be performed to enable informed consent

・Documents include the following: (1) period of storage of specimens, (2) maintenance of residual specimens, (3) disposal method, (4) possibility of re-examination with specimens (for example, because of significant advances in knowledge and technology), (5) possibility of secondary use under anonymity for the purpose of quality control, (6) possibility of access to the specimen by a third party, and (7) confidentiality protection method (symbolization/anonymization)

[Note]
International declarations and agreements on informed consent include the "Universal Declaration on Human Genome and Human Rights," "International Declaration on Human Genetic Information," and "Universal Declaration on Bioethics and Human Rights."

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5.4 Pre-examination handling, preparation and storage, collection

5.4.2 Information for patients and users

Laboratory services

Importance of provision of patient and family information

The analysis results found using NGS include the "primary findings" that are the main purpose of the test and "secondary findings" described below. The main purpose of the test must be explained slowly and in detail to the subject; it is also necessary to explain in advance that secondary findings may occur that improve the understanding of the subject.

5.4 Pre-examination handling, preparation and storage, collection

5.4.3 Request form information

Request form or an electronic:

e) Clinically relevant information about the patient and request, for examination performance and result interpretation purposes

The laboratory confirms that the testing request is appropriate and, if necessary, informs the subject that information on the subject/family is required to correctly interpret the test result.

[Note]

The significance of test results often depends on the accuracy and appropriateness of the information provided to the laboratory. All information necessary to conduct the testing, including the transportation status of the sample (specimen) to the laboratory, is sent to the laboratory with the sample (specimen).

5.4 Pre-examination handling, preparation and storage, collection

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5.4.4.1 General

Documented procedures for proper collection and handling of primary samples.

According to the purpose of the test, the collection and storage procedures to ensure the quality of each type of primary sample (specimen) shall be clarified.

[Note 1]

The following shows typical primary samples according to the purpose of the test.

1. Nucleic acid tests for pathogens: serum, plasma, urine, sputum, feces, etc.
2. Molecular tests for human somatic gene alterations: tissue, blood (white blood cells), plasma, bone marrow, urine (sediment), sputum
3. Human genetic testing: blood (white blood cells), oral mucosa, hair, nails, blood stains, umbilical cord

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5.4 Pre-examination handling, preparation and storage, collection

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5.4.4.1 General

Documented procedures for proper collection and handling of primary samples.

[Note 2]

Recommendation (draft): Reduction to the patients using biobank samples

1. Reduction to the patients using biobank samples is premised on a quality assurance mechanism.
2. There are documented policies and procedures to ensure the quality of the sample.
3. Refer to the following for the quality control and assurance of biobanks for clinical use:
   Domestic standard documents: Japanese Society of Pathology, JCCLS, etc.
   Foreign standards: ISO 15189 standard documents related to pre-measurement processes: ISO 20658 related to collection, ISO 20166, ISO20184, ISO 20186, and ISO 21474, etc. related to specimen/nucleic acid (ISO 15189 guidance document)

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5.4 Pre-examination handling, preparation and storage, collection

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5.4.4.1 General

Documented procedures for proper collection and handling of primary samples.

[Note 2]

Recommendation (draft): Reduction to the patients using biobank samples

4. A (anatomic) laboratory with a clinical biobank should undergo a bank function inspection by a third-party certification (ISO 15189, etc.) as a mechanism for quality assurance.
5. When returning samples and information to patients at the research biobank, it is considered whether to comply with the above 2 and 3, how to deal with these requirements and reflect the report (impact on the test results, test limits, etc.) in cooperate with the above 4 third-party certified laboratories.

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5.4 Pre-examination handling, preparation and storage, collection

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5.4.4.2 Instructions for pre-collection activities

Laboratory's instructions for pre-collection

c) Type and amount of primary sample to be collected with descriptions of the primary sample containers and any necessary additive

The container for the primary sample (specimen) for molecular tests and necessary additives are appropriately selected according to the purpose of tests (nucleic acid tests for pathogens, molecular tests for human somatic gene alterations, human genetic test) and type of sample (blood, plasma, urine, tissue, etc.).

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5.4 Pre-examination handling, preparation and storage, collection

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5.4.4.2 Instructions for pre-collection activities

Laboratory's instructions for pre-collection

d) Specific timing of collection, where needed

When collecting liquid-based cytology specimens, appropriate collection methods that can sufficiently collect the target cells are instructed and described.

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5.4 Pre-examination handling, preparation and storage, collection

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5.4.4.2 Instructions for pre-collection activities

Laboratory's instructions for pre-collection

e) Clinical information relevant to or affecting sample collection, examination performance, or result interpretation (e.g., history of drug administration)

- Although the intended use of the specimen is not always known, the specimens are typically stored for use in a wide range of molecular tests by understanding the variable factors affecting the specimen quality.
- In cytogenetical tests of tumor cells, there are instructions on the timing of sample (specimens) collection, such as collection before administration of anticancer drugs.

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5.4 Pre-examination handling, preparation and storage, collection

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5.4.4.3 Instructions for collection activities

Laboratory's instructions for collection activities

b) Verification that the patient meets pre-examination requirements
fasting status, medication status, sample collection at predetermined time or time intervals, etc.

- In nucleic acid tests for pathogens (virus tests), it is important to collect appropriate specimen materials at the appropriate stage to conduct accurate tests.

5.4 Pre-examination handling, preparation and storage, collection

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5.4.4.3 Instructions for collection activities

Laboratory's instructions for collection activities

c) Instructions for collection of primary blood and non-blood samples, with descriptions of the primary sample containers and any necessary additives;

- The container for the primary sample (specimen) for molecular tests and necessary additives are appropriately selected according to the purpose of the tests (nucleic acid tests for pathogens, molecular tests for human somatic gene alterations, human genetic test) and sample type (blood, plasma, urine, tissue, etc.).

5.4 Pre-examination handling, preparation and storage, collection

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5.4.4.3 Instructions for collection activities

Laboratory's instructions for collection activities

d) In situations where the primary sample is collected as part of clinical practice, information and instructions regarding primary sample containers, any necessary additives, and any necessary processing and sample transport

* communicate to the appropriate clinical staff

- The primary sample (specimen) container, necessary additives, transportation conditions, etc. are documented, instructed, and explained.

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5.4 Pre-examination handling, preparation and storage, collection

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5.4.4.3 Instructions for collection activities

Laboratory's instructions for collection activities

e) Instructions for labeling of primary samples in a manner that provides an unequivocal link with the patients from whom they are collected;

- Specimen storage containers should be uniquely identified and managed using barcodes (1D, 2D, etc.) or an RFID to accurately track and guarantee specimens. When barcodes are unique and easy to read, many downstream processes can be automated, avoiding the risk of human error.

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5.4 Pre-examination handling, preparation and storage, collection

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5.4.4.3 Instructions for collection activities

Laboratory's instructions for collection activities

g) Instructions for proper storage conditions before collected samples are delivered to the laboratory

- The responsible person for sample collection is notified of how to handle and store the various collected samples (specimens).
- Appropriate storage conditions (temperature, storage container) for molecular tests of primary samples (specimens) are established. The extracted RNA is rarely unstable. The storage containers are considered for the adsorption of nucleic acids.

5.4 Pre-examination handling, preparation and storage, collection

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5.4.5 Sample transportation

Laboratory's instructions for post-collection activities

> Packaging of samples for transportation
> Documented procedure for monitoring the transportations of samples

- Appropriate transport methods and transport temperature control (freezing, refrigeration, room temperature) are established and documented according to the molecular test samples (specimens).

5.4 Pre-examination handling, preparation and storage, collection

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5.4.5 Sample transportation

Documented procedure for monitoring the transportations of samples:

b) Within a temperature interval specified for sample collection and handling and with the designated preservatives to ensure the integrity of samples

- Appropriate storage conditions and storage temperature for molecular tests samples (specimens) are established.

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5.4 Pre-examination handling, preparation and storage, collection

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5.4.6 Sample reception

Laboratory's procedure for sample

a) Samples are unequivocally traceable, by request and labeling, to an identified patient or site.

- The history of specimen collection, storage, and transportation are tracked.

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5.4 Pre-examination handling, preparation and storage, collection

5.4.6 Sample reception

Laboratory's procedure for sample

b) Laboratory-developed and documented criteria for acceptance or rejection of samples are applied

- The received sample is evaluated to determine whether it is suitable for the intended testing.
- Criteria for rejecting samples (specimens), such as confirming inappropriate collection containers or storage conditions, that affect the results are established.

5.4 Pre-examination handling, preparation and storage, collection

5.4.6 Sample reception

Laboratory's procedure for sample

d) All samples received are recorded in an accession book, worksheet, computer, or other comparable system.

Record: Date and time of receipt and/or registration of samples

Record: Identity of the person receiving the sample

- The receipt of samples is recorded reliably.

5.4 Pre-examination handling, preparation and storage, collection

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5.4.7 Pre-examination handling, preparation and storage

Procedures and appropriate facilities

> for securing patient samples and avoiding deterioration, loss, or damage during pre-examination activities during handling, preparation, and storage

> time limits for requesting additional examinations or further examinations of the same primary sample

- There is the procedure to follow if there are deviations in the storage temperature limits.
- When a medical institution refers molecular tests using a pathological specimen to a registered clinical laboratory, the medical institution or registered clinical laboratory may gross the specimen. When grossing in a registered clinical laboratory, when the medical institution submits the pathological specimen to the registered clinical laboratory, the medical doctor gives specific instructions on the part to be grossed. Based on this, the registered clinical laboratory performs grossing and confirms that the grossing is conducted according to the instructions.

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5.4 Pre-examination process standards

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5.4 Pre-examination process standards

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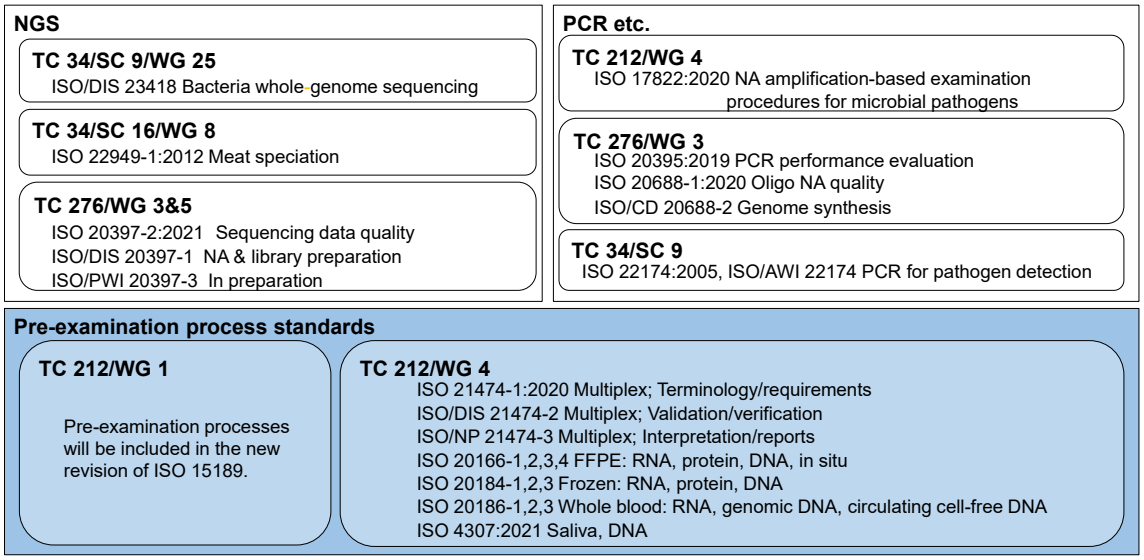

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5.4 Pre-examination process standards

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ISO 21474-1:2020

In vitro diagnostic medical devices — Multiplex molecular testing for nucleic acids — Part 1: Terminology and general requirements for nucleic acid quality evaluation

- This document provides the terms and general requirements for the evaluation of the quality of nucleic acids as the analytes for multiplex molecular tests, which simultaneously identify two or more nucleic acid target sequences of interest. This document is applicable to all multiplex molecular methods used for examination using in vitro diagnostic (IVD) medical devices and laboratory developed tests (LDTs). It provides information for both qualitative and quantitative detection of nucleic acid target sequences.
- This document is intended as guidance for multiplex molecular assays that detect and/or quantify human nucleic acid target sequences or microbial pathogen nucleic acid target sequences from human clinical specimens. This document is applicable to any molecular in vitro diagnostic examination performed by medical laboratories. It is also intended to be used by laboratory customers, in vitro diagnostics developers and manufacturers, biobanks, institutions and commercial organizations performing biomedical research, and regulatory authorities. This document is not applicable to metagenomics.
- NOTE An examination procedure developed for a laboratory's own use is often referred to as a "laboratory developed test", "LDT", or "in-house test".

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5.4 Pre-examination process standards

ISO 21474-2:2022

In vitro diagnostic medical devices — Multiplex molecular testing for nucleic acids — Part 2: Validation and Verification

- This document gives the general requirements for validation and verification of multiplex molecular tests which simultaneously identify two or more nucleic acid target sequences of interest. This document is applicable to all multiplex methods used for examination using IVD medical devices and laboratory developed tests (LDTs). It provides information for both qualitative and quantitative detection of nucleic acid target sequences.
- This document is intended as guidance for multiplex examinations that either detect and/or quantify human nucleic acid target sequences or microbial pathogen nucleic acid target sequences from human clinical specimens.
- This document is applicable to any molecular in vitro diagnostic (IVD) examination performed by medical laboratories. It is also intended to be used by laboratory customers, IVD developers and manufacturers, biobanks, institutions, and commercial organizations performing biomedical research and regulatory authorities. This document is not applicable to metagenomics.
- NOTE An examination procedure developed for a laboratory's own use is often referred to as a "laboratory developed test," "LDT," or "in-house test".

5.4 Pre-examination process standards

ISO 20166-1:2018

Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for formalin-fixed and paraffin-embedded (FFPE) tissue — Part 1: Isolated RNA

- This document gives guidelines on the handling, documentation, storage and processing of formalin-fixed and paraffin-embedded (FFPE) tissue specimens intended for RNA examination during the pre-examination phase before a molecular assay is performed.
- This document is applicable to molecular in vitro diagnostic examinations including laboratory developed tests performed by medical laboratories and molecular pathology laboratories. It is also intended to be used by laboratory customers, in vitro diagnostics developers and manufacturers, biobanks, institutions and commercial organizations performing biomedical research, and regulatory authorities.
- NOTE International, national or regional regulations or requirements can also apply to specific topics covered in this document.

5.4 Pre-examination process standards

ISO 20166-2:2018

Molecular in vitro diagnostic examinations — Specifications for pre-examinations processes for formalin-fixed and paraffin-embedded (FFPE) tissue — Part 2: Isolated proteins

- This document gives guidelines on the handling, documentation, storage and processing of formalin-fixed and paraffin-embedded (FFPE) tissue specimens intended for the examination of isolated proteins during the pre-examination phase before a molecular assay is performed.
- This document is applicable to molecular in vitro diagnostic examinations including laboratory developed tests performed by medical laboratories and molecular pathology laboratories. It is also intended to be used by laboratory customers, in vitro diagnostics developers and manufacturers, biobanks, institutions and commercial organizations performing biomedical research, and regulatory authorities.
- This document is not applicable for protein examination by immunohistochemistry.
- NOTE International, national or regional regulations or requirements can also apply to specific topics covered in this document.

5.4 Pre-examination process standards

ISO 20166-3:2018

Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for formalin-fixed and paraffin-embedded (FFPE) tissue — Part 3: Isolated DNA

- This document gives guidelines on the handling, documentation, storage and processing of formalin-fixed and paraffin-embedded (FFPE) tissue specimens intended for DNA examination during the pre-examination phase before a molecular assay is performed.
- This document is applicable to molecular in vitro diagnostic examinations including laboratory developed tests performed by medical laboratories and molecular pathology laboratories. It is also intended to be used by laboratory customers, in vitro diagnostics developers and manufacturers, biobanks, institutions and commercial organizations performing biomedical research, and regulatory authorities.
- NOTE International, national or regional regulations or requirements can also apply to specific topics covered in this document.

5.4 Pre-examination process standards

ISO 20166-4:2021

Molecular in vitro diagnostic examinations — Specifications for preexamination processes for formalin-fixed and paraffin-embedded (FFPE) tissue — Part 4: In situ detection techniques

- This document specifies requirements and gives recommendations for the collection, handling, documentation, transport, storage and processing during the pre-examination phase of formalin-fixed and paraffin-embedded (FFPE) tissue specimens intended for qualitative and/or (semi-)quantitative in situ examination of the morphology and of biomolecules, such as metabolites, proteins, DNA and/or RNA, on FFPE tissue sections by using different in situ detection techniques.
- This document is applicable to in vitro diagnostic examinations using in situ detection techniques. These include laboratory developed tests performed by pathology laboratories (histopathology laboratories) as well as by molecular pathology laboratories and other medical laboratories. It is also intended to be used by laboratory customers, in vitro diagnostics developers and manufacturers, biobanks, as well as institutions and commercial organizations performing biomedical research, and regulatory authorities.
- This document is not applicable to the pre-examination phase of RNA, proteins and DNA isolated from FFPE tissue for examination. These are covered in ISO 20166-1, ISO 20166-2 and ISO 20166-3, Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for isolated RNA, proteins and DNA, respectively.
- Different dedicated measures are taken for pre-examination processes for fine needle aspirates (FNAs). These are covered in CEN WI 00140128, CEN WI 00140126, and CEN WI 00140129, Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for Fine Needle Aspirates (FNAs) isolated cellular RNA, isolated proteins, and isolated genomic DNA, respectively.
- NOTE International, national or regional regulations or requirements can also apply to specific topics covered in this document.

5.4 Pre-examination process standards

ISO 20184-1:2018

Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for frozen tissue — Part 1: Isolated RNA

- This document gives guidelines on the handling, documentation, storage and processing of frozen tissue specimens intended for RNA examination during the pre-examination phase before a molecular assay is performed.
- This document is applicable to any molecular in vitro diagnostic examination performed by medical laboratories and molecular pathology laboratories that evaluate RNA extracted from frozen tissue. It is also intended to be used by laboratory customers, in vitro diagnostics developers and manufacturers, biobanks, institutions and commercial organisations performing biomedical research, and regulatory authorities.
- Tissues that have undergone chemical stabilization pre-treatment before freezing are not covered in this document.
- NOTE International, national or regional regulations or requirements can also apply to specific topics covered in this document.

5.4 Pre-examination process standards

ISO 20184-2:2018

Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for frozen tissue — Part 2: Isolated proteins

- This document gives guidelines on the handling, documentation, storage and processing of frozen tissue specimens intended for the examination of isolated proteins during the pre-examination phase before a molecular assay is performed.
- This document is applicable to any molecular in vitro diagnostic examination performed by medical laboratories and molecular pathology laboratories that evaluate proteins isolated from frozen tissue. It is also intended to be used by laboratory customers, in vitro diagnostics developers and manufacturers, biobanks, institutions and commercial organisations performing biomedical research, and regulatory authorities.
- NOTE International, national or regional regulations or requirements can also apply to specific topics covered in this document.

5.4 Pre-examination process standards

ISO 20184-3:2021

Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for frozen tissue — Part 3: Isolated DNA

- This document specifies requirements and gives recommendations for the handling, storage, processing, and documentation of frozen tissue specimens intended for DNA examination during the pre-examination phase before a molecular examination is performed.
- This document is applicable to molecular in vitro diagnostic examinations including laboratory developed tests performed by medical laboratories and molecular pathology laboratories that evaluate DNA isolated from frozen tissue. It is also intended to be used by laboratory customers, in vitro diagnostics developers and manufacturers, biobanks, institutions and commercial organizations performing biomedical research, and regulatory authorities.
- Tissues that have undergone chemical stabilization pre-treatment before freezing are not covered in this document.
- NOTE International, national, or regional regulations or requirements can also apply to specific topics covered in this document.

5.4 Pre-examination process standards

ISO 20186-1:2019

Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for venous whole blood — Part 1: Isolated cellular RNA

- This document gives guidelines on the handling, storage, processing and documentation of venous whole blood specimens intended for cellular RNA examination during the pre-examination phase before a molecular examination is performed. This document covers specimens collected in venous whole blood collection tubes.
- This document is applicable to any molecular in vitro diagnostic examination performed by medical laboratories. It is also intended to be used by laboratory customers, in vitro diagnostics developers and manufacturers, biobanks, institutions and commercial organizations performing biomedical research, and regulatory authorities.
- Different dedicated measures are taken for stabilizing blood cell free circulating RNA and RNA in exosomes circulating in blood. These are not described in this document.
- Different dedicated measures are taken for collecting, stabilizing, transporting and storing capillary blood as well as for collecting and storing blood by paper based technologies or other technologies generating dried blood. These are not described in this document.
- This document does not cover the isolation of specific blood cells and subsequent isolation of cellular RNA therefrom.
- RNA in pathogens present in blood is not covered by this document.

5.4 Pre-examination process standards

ISO 20186-2:2019

Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for venous whole blood — Part 2: Isolated genomic DNA

- This document gives guidelines on the handling, storage, processing and documentation of venous whole blood specimens intended for genomic DNA examination during the pre-examination phase before a molecular examination is performed. This document covers specimens collected in venous whole blood collection tubes.
- This document is applicable to any molecular in vitro diagnostic examination performed by medical laboratories. It is also intended to be used by laboratory customers, in vitro diagnostics developers and manufacturers, biobanks, institutions and commercial organizations performing biomedical research, and regulatory authorities.
- Different dedicated measures are taken for stabilizing blood cell free circulating DNA, which are not described in this document.
- NOTE Circulating cell free DNA in blood is covered in ISO 20186-3.
- Different dedicated measures are taken for collecting, stabilizing, transporting and storing capillary blood as well as for collecting and storing blood by paper based technologies or other technologies generating dried blood. These are not described in this document.
- This document does not cover the isolation of specific blood cells and subsequent isolation of genomic DNA therefrom.
- DNA in pathogens present in blood is not covered by this document.

5.4 Pre-examination process standards

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ISO 20186-3:2019

Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for venous whole blood — Part 3: Isolated circulating cell free DNA from plasma

- This document provides recommendations and requirements on the handling, storage, processing and documentation of venous whole blood specimens intended for circulating cell free DNA (ccfDNA) examination during the pre-examination phase before an analytical test is performed. This document covers specimens collected in venous whole blood collection tubes.
- This document is applicable to any molecular in vitro diagnostic examination performed by medical laboratories. It is also intended to be used by laboratory customers, in vitro diagnostics developers and manufacturers, biobanks, institutions and commercial organizations performing biomedical research, and regulatory authorities.
- Different dedicated measures are taken for stabilizing blood genomic DNA, which are not described in this document. Blood genomic DNA is covered in ISO 20186-2.
- Different dedicated measures are taken for preserving DNA in circulating exosomes, which are not described in this document.
- NOTE ccfDNA obtained from blood by the procedures cited in this document can contain DNA originally present in exosomes[8][9].
- DNA in pathogens present in blood is not covered by this document.

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5.4 Pre-examination process standards

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ISO 4307:2021

Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for saliva — Isolated human DNA

- This document specifies requirements and recommendations on the handling, storage, processing and documentation of saliva specimens intended for human DNA examination during the pre-examination phase before a molecular examination is performed.
- This document is applicable to molecular in vitro diagnostic examination including laboratory developed tests performed by medical laboratories. It can also be used by laboratory customers, in vitro diagnostics developers and manufacturers, biobanks, institutions and commercial organizations performing biomedical research, and regulatory authorities.
- Dedicated measures that need to be taken for saliva collected on absorbing material or by mouth washes are not described in this document. Neither are measures for preserving and handling of native saliva cell-free DNA, pathogens, and other bacterial or whole microbiome DNA in saliva described.
- NOTE International, national or regional regulations or requirements can also apply to specific topics covered in this document.

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Biobank considerations

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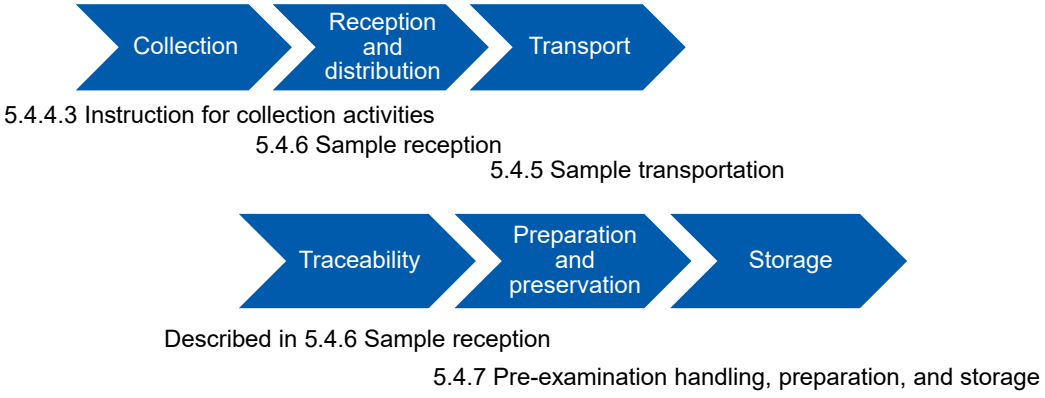
Biobank considerations

Biobank in ISO 15189

ISO 15189 requirements cover all processes for biobanking of human samples.



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Biobank considerations

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ISO 20387:2018

- ISO 20387:2018 Biotechnology -- Biobanking -- General requirements for biobanking.
- → Published in August 2018

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Biobank considerations

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ISO 20387:2018

1 Scope
2 Normative references
3 Terms and definitions
4 General requirements
- 4.1 General
- 4.2 Impartiality
- 4.3 Confidentiality

5 Structural requirements
6 Resource requirements
- 6.1 General
- 6.2 Personnel
- 6.3 Facilities/dedicated areas and environmental conditions
- 6.4 Externally provided processes, products, and services
- 6.5 Equipment

Biobank-specific

7 Process requirements
- 7.1 General
- 7.2 Collection of biological material and associated data
- 7.3 Reception and distribution of biological material and associated data
- 7.4 Transport of biological material and associated data
- 7.5 Traceability of biological material and associated data
- 7.6 Preparation and preservation of biological material
- 7.7 Storage of biological material
- 7.8 Quality control of biological material and associated data
- 7.9 Validation and verification of methods
- 7.10 Management of information and data
- 7.11 Nonconforming output
- 7.12 Report requirements
- 7.13 Complaints

Biobank-specific

8 Quality management system requirements
- 8.1 Options
- 8.2 Documented information for the quality management system (Option A)
- 8.3 Control of quality management system documents (Option A)
- 8.4 Control of records (Option A)
- 8.5 Actions to address risks and opportunities (Option A)
- 8.6 Improvement (Option A)
- 8.7 Corrective action for nonconforming output (Option A)
- 8.8 Internal audits (Option A)
- 8.9 Quality management reviews (Option A)

Aligned with ISO 9001

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Biobank considerations

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ISO 20387:2018

1 Scope
2 Normative references
3 Terms and definitions
4 General requirements
- 4.1 General
- 4.2 Impartiality
- 4.3 Confidentiality

5 Structural requirements
6 Resource requirements
- 6.1 General
- 6.2 Personnel
- 6.3 Facilities/dedicated areas and environmental conditions
- 6.4 Externally provided processes, products, and services
- 6.5 Equipment

General, structure & resources

7 Process requirements
- 7.1 General
- 7.2 Collection of biological material and associated data
- 7.3 Reception and distribution of biological material and associated data
- 7.4 Transport of biological material and associated data
- 7.5 Traceability of biological material and associated data
- 7.6 Preparation and preservation of biological material
- 7.7 Storage of biological material
- 7.8 Quality control of biological material and associated data
- 7.9 Validation and verification of methods
- 7.10 Management of information and data
- 7.11 Nonconforming output
- 7.12 Report requirements
- 7.13 Complaints

Biobanking processes

8 Quality management system requirements
- 8.1 Options
- 8.2 Documented information for the quality management system (Option A)
- 8.3 Control of quality management system documents (Option A)
- 8.4 Control of records (Option A)
- 8.5 Actions to address risks and opportunities (Option A)
- 8.6 Improvement (Option A)
- 8.7 Corrective action for nonconforming output (Option A)
- 8.8 Internal audits (Option A)
- 8.9 Quality management reviews (Option A)

QMS
(Quality management system)

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Biobank considerations

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BMaD in TR 22758

BMaD

- Biological Material and Associated Data
  Both are inseparable from each other in biobanking.
- TR 22758
  Guidance to biobanks on how to implement the quality management, management, and technical requirements of ISO 20387.
- BMaD in TR 22758
  BMaD: ISO 20387 defines biological material (3.7) and associated data (3.3). For the purpose of this document the terms are combined as "biological materials and/or associated data" (BMaD).

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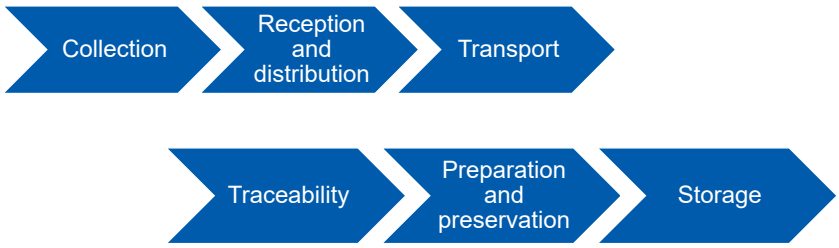
Biobank considerations

Biobanking processes



Requirements in ISO 20387 cover all process of biobanking from collection to storage of BMaD.

Biobank considerations

7.2 Collection of BMaD

- 7.2.1.1
  - When the biobank is responsible for the collection of biological material,
  - Define and document: information related to the collection of the biological material
- 7.2.3.1
  - The collection procedure shall be defined
  - by the biobank and/or recipient/user,
  - according to the intended use of the biological material, proven techniques, or relevant standards.

Biobank considerations

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7.3 Reception and distribution of BMaD

- 7.3.1.1
  - The principles governing access to and distribution of biological material and associated data:
  - Defined, documented, and, where relevant, published.
- 7.3.2 Reception
  - 7.3.2.1
  - Document and implement procedures for receiving or acquiring BMaD
  - e.g., internal transfers or external shipments/transfers
- 7.3.3 Distribution
  - The distribution and any exchange of BMaD with the biobank's access principles (see 7.3.1.1), reporting specifications (see 7.12), and in compliance with other relevant requirements
  - e.g., material transfer agreement (MTA), data transfer agreement (DTA)

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Biobank considerations

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7.4 Transport of BMaD

- 7.4.1
  - Establish, document, and implement procedures
    - for shipping and receiving BM
      - appropriate conditions for the continued maintenance of BM integrity…
- 7.4.2
  - The biobank shall maintain a critical chain of custody records
    - for all BM from the point of dispatch to the point of receipt
  - chain of custody
    - responsibility for or control of materials and associated data as they move through each step of a process

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Biobank considerations

7.5 Traceability of BMaD

- 7.5.1
  - The biobank shall ensure the traceability of the BMaD from collection, acquisition, or reception to distribution, disposal, or destruction, as follows:
    - Traceability
      - ability to trace the history, application, or location of an object
    - (Detailed description has introduced in an example.)

Biobank considerations

7.6 Preparation and preservation of BM

- 7.6.1
  - The method(s) of preparation and/or preservation
    - Defined according to an evidence-based documented processing method
      - e.g., an International Standard
    - or specify in agreement with the provider/recipient/user.

Biobank considerations

7.7 Storage of BM

- 7.7.2
  - Documented procedures for the storage and tracking of biological material:
    a. the tagging information
       at least the unique identifier of the biological material
    b. the type of container and environmental conditions
       for the biological material storage
    c. mechanism(s) for traceability
    d. a short-term back-up plan
       for maintaining accurate storage conditions/temperatures in the case of emergency challenges in maintaining defined storage conditions

Biobank considerations

7.7 Storage of BM

- 7.7.3
  - Critical activities during storage
    - Processing parameters shall be measured, monitored, and documented.
- 7.7.4
  - Verify the storage location of BMaD
    - Traceability of each biological material and each storage transaction shall be ensured at all times.
- 7.7.7
  - Verify the biological material inventory at planned intervals using a defined procedure

Biobank considerations

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What is Quality?

- 3.6.2 Quality
  - Degree to which a set of inherent characteristics of an object fulfils requirements [ISO 9001:2015]
- Quality cannot be discussed when the requirements are unclear.
- 3.24 Fitness for intended purpose (fit for purpose)
  - In line with prearranged requirements for an intended use [ISO 20387:2018]
- Quality sought by biobanks is the degree to which BMaD fitting for intended purpose fulfils prearranged requirements…

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Biobank considerations

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7.8.2 Quality control of processes

- 7.8.2.1
  The biobank shall establish, document, and implement procedures specifying QC activities throughout the biobanking processes, including QC criteria corresponding to predefined specifications, to demonstrate the fitness for the intended purpose of the biological material and associated data.
- What shall biobank do in advance
  - Define intended purpose
  - Define specification
  - Document the procedure of QC activities

Specification shall be defined in line with the intended purpose

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Biobank considerations

Monitoring and Measurement

- During the execution of critical activities performed during storage, relevant processing parameters shall be measured, monitored, and documented.
- Time stamp
  - The date and, where necessary, the time(s) of critical activities during storage, and personnel accessing the biological record for each biological material
- Date and time format: ISO 8601

Biobank considerations

Validation and Verification

- 7.9 Validation and verification of methods
- 7.9.1 General
  - Use validated and/or verified methods for critical activities
    - according to 7.9.2 (Validation) and 7.9.3 (Verification) at all stages of the biological material life cycle

Definitions of key terms

3.52 Validation

confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

3.53 Verification

confirmation, through the provision of objective evidence, that specified requirements have been fulfilled

Biobank considerations

7.9.2 Validation

- 7.9.2.1 Methods for critical activities
  - Validated, to ensure fitness for the intended purpose
    - Record results, procedure used for the validation
    - Record statement on whether the method is fit for purpose
- 7.9.2.2 Validation as extensive as necessary
  - Provision of objective evidence (in the form of performance characteristics)
  - Specific requirements for the intended use have been fulfilled
- 7.9.2.3 When changes the validated method
  - The impact of such changes shall be documented
  - When appropriate, a new validation shall be carried out

Biobank considerations

7.9.3 Verification

- 7.9.3.1 Validated methods used without modification
  - → Verification by the biobank before being used
- 7.9.3.2 The verification confirms that the set criteria for the method have been met according to the specification.
  - Obtaining objective evidence (in the form of performance characteristics)
- 7.9.3.3 Record (document)
  - Procedure used for verification
  - Results obtained

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Personnel requirements for biobank

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Personnel requirements for biobank

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- 6.2.2 Competence and Competence Assessment
- 6.2.2.1 Competence Requirement
  - Define and document the competence required for personnel involved in biobank activities
- 6.2.2.2 Ensuring Competence
  - Appropriate education, training, demonstrated skills, and/or experience necessary to perform assigned duties and activities are required
- 6.2.2.3 Documented information
  - Maintain documented information for personnel including appropriate professional competence and education/training
- 6.2.2.4 Competence Assessment
  - Competence assessment according to the biobank's established criteria
- 6.2.2.5 Regular assessment
  - Regular relevant assessment for personnel to determine the requirements to acquire and retain their necessary competence

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Personnel requirements for biobank

Qualification

ISBER/QBRS

- **Qualification in Biorepository Science**

- ISBER and ASCP BOC are pleased to announce a new Qualification in Repository Science (QBRS) for biobankers
- https://www.isber.org/page/qualification
- Upon meeting specific educational and experience requirements for the qualification, candidates will be eligible to complete an online examination and, if successful, gain recognition for their skills and competencies as biobankers. This new qualification will further advance the field of biorepository science! Biobanks are vital to medical research and precision medicine and require qualified professionals to obtain high quality results that will be useful in advancing biomedicine.

CIBER/BiTA

- **Biorepository Technical Administrator Qualification**

- A Biorepository Technical Administrator (BiTA) is a personnel qualification that certifies expertise and technical capabilities of the biorepository field. Certification is given to the expertise of personnel active in the bio-repository field, the expertise such as understanding of biological sample handling techniques, operations in the utilization of biological resources, quality control, ethics, and international standards.
- BiTA was developed by Japanese KOLs for Japanese personnel. It is modeled after the Qualification in Biorepository Science (QBRS) conducted by ISBER. CIBER will further strengthen cooperation with ISBER and other related academic societies and organizations and will endeavor to bring BiTA test to serve as a requirement for ISO facility certification and various guidelines.

These qualification can be applied in competence assessment .

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Reference

- ISO 15189:2012
- ISO 15189 Guidance from JCCLS for molecular testing
- ISO 20387:2018

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