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Biotechnology — Biobanking — General requirements for the validation and verification of processing methods for biological material in biobanks

Biotechnologie — Biobanques — Exigences générales pour la validation et la vérification des méthodes de traitement du matériel biologique dans les biobanques

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

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For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 276, *Biotechnology*.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

Biobanks, producing viable and non-viable biological materials (human, animal, plant, microbial) for research purposes, within biotechnology, use processing methods. Many biobanks include processing laboratories where processing methods are performed and biological materials are produced as an output. Examples of widely used processing methods, applied by biobank laboratories, include DNA, RNA and protein extractions from blood, tissue, seeds, bacteria, or other biological material, or primary cell cultures. An example for the validation of a processing method is provided in Reference [27]. Biobank laboratories are not always equipped to perform testing methods, which are required for annotation or qualification of the biological material output.

This document sets out specific requirements for validation of processing methods. It is intended to help biobank laboratories who perform processing of biological materials, whether they perform themselves testing activities on the biological materials they have produced, or not. It enables validation of processing methods, complements the quality management system of any biobank laboratory performing processing of biological materials and gives more credibility to such an organization. It is understood that while the term "method" used in ISO/IEC 17025 corresponds to "testing method" or "calibration method", a fundamental distinction exists between "processing methods" where the output is a biological material and "testing methods" where the output is a test result (see Annex A). It is understood that validation of processing methods performed by accredited testing laboratories, who test the biological material output themselves, is already included in their accreditation scope.

Validation of a processing method encompasses confirmation of the fitness for purpose of the output biological material, assessment of the homogeneity and stability of the biological material, and assessment of the reproducibility and robustness of the processing method. This validation requires testing in order to assess/measure the qualitative or quantitative properties of the biological material. This testing will lead to the assessment of the fitness for purpose, the reproducibility, and the robustness of the processing method. Examples of such properties are: viability, purity, pluripotency, molecular integrity, concentration, growth capacity, etc.

Biotechnology — Biobanking — General requirements for the validation and verification of processing methods for biological material in biobanks

1 Scope

This document specifies the validation and verification requirements applicable to a biobank to be able to demonstrate that it operates its processing of biological materials with validated and/or verified methods that are fit for purpose.

This document is intended for use in the implementation and validation of processing methods for biological materials.

This document covers method validation and verification for the production of all biological materials. This document does not apply to biological material intended for food/feed production, laboratories undertaking food/feed analysis, and/or therapeutic use.

Reference material production is not covered in this document. For the production requirements for reference materials, see ISO 17034.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements 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 20387, *Biotechnology — Biobanking — General requirements for biobanking*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 20387 and the following apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

3.1
aliquot
portion of a quantity of biological material which has been divided into separate parts at the same time under identical conditions

Note 1 to entry: The aliquot is representative of the biological material with respect to the property or properties being investigated.

Note 2 to entry: The term aliquot most commonly refers to liquid or semi-liquid biological materials.

3.2
biobank laboratory
processing (3.15) laboratory under the control of a biobank where *processing methods* (3.16) are performed for the output/production of biological materials

3.3
exploratory processing method
processing method (3.16) or adaptation/modification of a processing method, at an early stage of development by the *biobank laboratory* (3.2) and for which further assessment is needed to determine if it is useful for a specified application

3.4
external provider
body that undertakes aspects of the collection, transportation, *preparation* (3.14), handling, *homogeneity* (3.7) and *stability* (3.21) assessment, testing or storage of the biological materials under its own management system, on behalf of the biobank, on a contractual basis, or in the context of the *validation* (3.25) of a *processing method* (3.16)

Note 1 to entry: A body can be an organization or a company, public or private.

3.5
feasibility
assessment of whether the *processing method* (3.16) can be applied to produce the desired type of biological material output, independently from the properties of interest of this output biological material

3.6
fit for purpose
fitness for the intended purpose
in-line with prearranged requirements for an intended use

Note 1 to entry: The definition of such requirements can take place within the biobank itself and/or in collaboration with users and should consider analytical and other relevant criteria.

Note 2 to entry: These requirements correspond to the *feasibility* (3.5) of the downstream intended use and the satisfaction of predefined *performance* (3.12) criteria of the intended use.

[SOURCE: ISO 20387:2018, 3.24, modified — Note 2 to entry has been added.]

3.7
homogeneity
uniformity of a specified, quantitative or qualitative, property value throughout a defined portion [or among different *aliquots* (3.1)] of a biological material

3.8
installation qualification
IQ
process of establishing by objective evidence that all key aspects of the process equipment and ancillary system installation comply with the approved specification

[SOURCE: ISO 11139:2018, 3.220.2]

3.9
measurand
quantity intended to be measured

[SOURCE: ISO/IEC Guide 99:2007, 2.3, modified — Notes to entry and examples were deleted.]

3.10
measurement
process of experimentally obtaining one or more quantity values that can reasonably be attributed to a quantity

Note 1 to entry: Measurement does not apply to nominal properties.

Note 2 to entry: Measurement implies comparison of quantities or counting of entities.

Note 3 to entry: Measurement presupposes a description of the quantity commensurate with the intended use of a measurement result, a measurement procedure, and a calibrated measuring system operating according to the specified measurement procedure, including the measurement conditions

[SOURCE: ISO/IEC Guide 99:2007, 2.1]

3.11
operational qualification
OQ
process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

[SOURCE: ISO 11139:2018, 3.220.3]

3.12
performance
set of properties of interest of a biological material, produced by a *processing method* (3.16), e.g. yield, purity, integrity, viability, functionality

3.13
performance qualification
PQ
process of establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements

[SOURCE: ISO 11139:2018, 3.220.4]

3.14
preparation
activities, taking place in a laboratory after acquisitioning, to make biological material ready for further use in the life cycle, storage or distribution

Note 1 to entry: These activities can include, e.g. determination of volume or weight, centrifugation, homogenization, purification, isolation, fixation, stabilization, filtration, sorting, culture, vacuum drying, freeze drying, fractionation, aliquoting, removing tissues, cutting / milling / shaping, washing / soaking with antibiotic or antimicrobial solutions, volume reduction / concentration, demineralization, glycerolisation, sterilization, controlled or uncontrolled freezing, vitrification, cryopreservation.

[SOURCE: ISO 20387:2018, 3.37, modified — Note 1 to entry was modified by adding more details.]

3.15
processing
performing any activity on biological material and associated data during all stages of the life cycle

[SOURCE: ISO 20387:2018, 3.36]

3.16
processing method
procedure, applied to biological material and/or associated data during *processing* (3.15), with potential to impact the intrinsic properties of the biological material and/or associated data produced as output

Note 1 to entry: A processing method can include, but is not limited to, activities belonging to: collection, *preparation* (3.14), preservation, storage.

Note 2 to entry: The whole or part of a processing method can be a standard method.

Note 3 to entry: The term “standard” in this instance refers to the broader definition of “standard” — i.e., an agreed-upon set of requirements.

Note 4 to entry: A simple processing method is a processing method that requires a simple laboratory manipulation (e.g. centrifugation of collection tubes or mechanical disruption of tissues) without the addition of chemical substances by the *biobank laboratory* (3.2) operator, and without cell disruption or cell selection as part of a multi-step process (e.g. preparation of plasma, serum, buffy coat).

Note 5 to entry: A complex processing method is a processing method that requires usage of multiple steps and/or addition of chemical substances by the biobank laboratory operator (e.g. preparation of DNA, RNA, proteins, nuclei and other organelles, cell lines).

Note 6 to entry: Qualitative or quantitative tests for the examination of properties/quality/quantity attributes of the produced biological material are outside of the scope of the "processing method" itself. However, a qualitative or quantitative test can be part of a "processing method" if it is necessary as an "in-process control" step during the processing method.

[SOURCE: ISO 20387:2018, 3.38, modified — The notes to entry were added.]

3.17
proficiency testing
evaluation of participant *performance* (3.12) against pre-established criteria by means of interlaboratory comparisons

[SOURCE: ISO/IEC 17043:2010, 3.7, modified — Notes to entry have been deleted.]

3.18
property of interest
physical, chemical, biological, or microbiological property or characteristic that describes or is an indicator of quality

3.19
reproducibility
<processing method> coefficient of variation (CV %) of a property value being measured in biological materials which are the *processing* (3.15) output from *aliquots* (3.1) of the same input biological material (e.g. volume, weight, concentration)

Note 1 to entry: The reproducibility of a *processing method* (3.16) includes components arising from the processing method itself and from the analytical uncertainty of the testing method used to assess the reproducibility.

Note 2 to entry: In general, for a given set of information, it is understood that the reproducibility of a processing method is associated with a stated *measurand* (3.9). A modification of this measurand and the testing method results in a modification of the associated reproducibility.

3.20
robustness
<processing method> capacity of a *processing method* (3.16) to produce biological materials whose properties remain within defined limits despite deviations from the experimental conditions that are described in the *standard operating procedure (SOP)* (3.22) of the processing method

3.21
stability
ability of a biological material, when stored under specified conditions, to maintain a specified property value within specified limits for a specified period of time

[SOURCE: ISO Guide 30:2015, 2.1.15, modified — The words "reference material" have been replaced by "biological material" and Note 1 to entry has been deleted.]

3.22
standard operating procedure
SOP
written procedure prescribed for repetitive use as a practice, in accordance with agreed-upon specifications aimed at obtaining a desired outcome

3.23
standard processing method
method officially accepted and recognized described in unambiguous details and validated for a stated purpose

Note 1 to entry: Standard processing methods include e.g. methods published by a standardization body or approved by regulatory authorities or published in peer-reviewed scientific literature, dedicated, at least partly, to the *validation* (3.25) of the method.

Note 2 to entry: The term "standard" in this instance refers to the broader definition of "standard"—i.e., an agreed-upon set of requirements.

3.24
stress
intentional exposure of biological material to conditions that are different from the predefined routine conditions or procedures and that can affect the properties of the biological material

3.25
validation
confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

Note 1 to entry: The objective evidence needed for a validation is the result of a test or other form of determination such as performing alternative calculations or reviewing documents.

Note 2 to entry: The word "validated" is used to designate the corresponding status.

Note 3 to entry: The use conditions for validation can be real or simulated.

Note 4 to entry: Validation is the confirmation that the specifications announced by the *biobank laboratory* (3.2) are met.

[SOURCE: ISO 9000:2015, 3.8.13, modified — Note 4 to entry was added.]

3.26
verification
confirmation, through the provision of objective evidence, that specified requirements have been fulfilled

Note 1 to entry: Verification is the confirmation that the specifications announced by a supplier, a publication or another external source are met.

Note 2 to entry: The objective evidence needed for a verification can be the result of an inspection or of other forms of determination such as performing alternative calculations or reviewing documents.

Note 3 to entry: The activities carried out for verification are sometimes called a qualification process.

Note 4 to entry: The word "verified" is used to designate the corresponding status.

[SOURCE: ISO 9000:2015, 3.8.12, modified — Note 1 to entry was added.]

4 Abbreviated terms

Abbreviated term	Explanation
CPT	cell preparation tube
CV	coefficient of variation
Hly	hemolysin
n	number of samples
M	mean square
OD	optical density

Abbreviated term	Explanation
PBMC	peripheral blood mononuclear cells
PCA	principal component analysis
RT	room temperature
u	variance
S	standard deviation
SOP	standard operating procedure

5 General and resource requirements

The biobank shall establish, implement and maintain a documented quality management system. (See e.g. ISO 9001 or ISO 20387:2018, Clause 8.)

Requirements relative to personnel, infrastructure and environmental conditions, and processing equipment are described in ISO 20387 and shall be followed.

6 Selection of processing methods

6.1 The methods for processing of biological materials shall meet the specified requirements for the intended use and/or the needs of the customer (depositor or recipient). When the intended use is not known beforehand, the biobank laboratory shall define a perimeter of intended uses (e.g. DNA-based tests).

6.1.1 When the customer (depositor or recipient) does not specify the processing method to be used, the biobank laboratory shall select processing methods that have been published either in international, regional or national standards, or by reputable technical organizations, or in relevant scientific texts or journals, or as specified by the manufacturer of the equipment / commercial kit, and that are deemed fit for purpose.

6.1.2 The biobank laboratory shall ensure that it uses the latest valid edition of a standard and/or user manual, unless it is not appropriate or feasible to do so. Whenever necessary, the standard shall be supplemented with additional details to ensure consistent application.

6.2 Biobank laboratory-developed methods or methods adopted by the biobank laboratory can also be used if they are appropriate for the intended use and are validated. The customer shall be informed, upon their request, as to the specifications of the method chosen, which constitute critical elements of the method, and as to the scope of its validation by the biobank laboratory.

When a customer requests implementation of an exploratory processing method, or the implementation of a method of processing for rare biological material types, the customer can accept that the method is not validated or that the method is validated using surrogate materials. Such acceptance shall be documented. If any report based on an exploratory processing method or methods that otherwise lack conclusive validation evidence is issued by the biobank, the lack of assurance of its fitness for purpose and the acceptance of the processing method by the client shall be stated.

6.3 The biobank shall inform the customer when the method proposed by the customer is considered to be inappropriate for the intended use or out of date.

6.4 A description and the performance specifications of the selected processing methods shall be documented.

7 Processing method implementation

7.1 Targets for method implementation

7.1.1 The biobank laboratory shall define and document the performance requirements for the implementation of every processing method that will be validated (see 6.1).

7.1.2 When implementing a processing method developed or adopted by the biobank laboratory, the scope in terms of types of intended downstream analytical or other uses shall be defined and considered, in order to ensure that the method is fit for purpose.

7.2 Processing method implementation

7.2.1 The biobank laboratory shall implement standard processing methods only after verification and a statement of compliance, issued by competent staff from the biobank laboratory, for all predetermined requirements. All verification related records and statements issued by the biobank laboratory, shall be maintained for a predefined period of time.

7.2.2 For non-standard processing methods, the first step for the implementation of a processing method is a feasibility assessment.

7.2.2.1 The feasibility assessment shall be done in case of a biobank laboratory-developed or a modified standard processing method.

NOTE The objective of the feasibility assessment is to determine if the planned method is feasible.

7.2.2.2 Biological materials that are used in feasibility studies shall be of the same or similar type to those that will ultimately be used with the method. Pooled biological material can be used.

7.2.2.3 Detailed records of the techniques/methods used and the results shall be maintained. The output of the feasibility study shall be a preliminary version of an SOP.

7.2.3 The second step for non-standard processing methods is the optimization of the method.

7.2.3.1 Optimization applies to biobank laboratory-developed methods or to standard methods that have been modified by the biobank laboratory.

7.2.3.2 Relevant parameters of the method shall be defined and optimized following an experimental plan. The definition of these parameters shall be based on a risk-based approach, according to the specific method (e.g. centrifugation speed, elution time and/or temperature, fixation time). The optimization parameters, the experimental plan, and the data analysis procedures shall be documented. Plans shall be updated as implementation proceeds and effective communication amongst all personnel involved shall be ensured.

7.2.3.3 The results and conclusions shall be documented. The output of the optimization study shall be an updated version of the SOP released for validation.

8 Initial validation of a processing method

8.1 General

The validation of a method is the procedure by which the biobank laboratory shows, with experimental and documented evidence, that the method is fit for purpose. Method validation shall be performed by trained and competent personnel (e.g. specifically trained, experienced, board certified or qualified personnel) according to a validation plan with predefined acceptance criteria.

8.2 Validation plan

The validation plan shall focus on the critical sources of variation in the performance of the method. The validation plan shall be documented, including the specific validation conditions and acceptance criteria for a given method. The plan shall be reviewed and approved by competent personnel.

The validation plan should contain the following information:

a) scope of the method;

b) description of the type of biological material that is the output of the method to be validated;

c) properties of interest to be determined on the output biological materials (by the biobank laboratory or by an external provider);

d) description of the apparatus and equipment for the processing, including technical performance requirements;

e) list of the trained/competent staff;

f) control materials that can be required;

g) environmental conditions that can be required;

h) description of the SOP, including:

   1) identification of biological materials;

   2) checks to be made before the processing work is started;

   3) checks that the equipment is working properly and, where required, calibration and adjustment of the equipment before each use;

   4) the method of recording the processing steps;

   5) any safety measures to be observed (for operators and/or for biological materials);

i) criteria and/or requirements for approval/rejection;

j) data to be recorded;

k) the statistical procedures for estimating reproducibility, robustness, homogeneity and stability (examples can be found in Annex B).

8.3 Assays for properties of interest

8.3.1 The critical properties of interest shall be identified and documented. These shall be assessed by relevant assays.

8.3.2 The assays shall be performed either by the biobank laboratory or by external providers. The assays shall be performed by trained and competent personnel, e.g. according to ISO/IEC 17025.

NOTE Examples of assays that can be used to assess the quality of the processed biological materials are: bacterial and fungi viability, seed viability, gene expression tests, NGS tests, metabolite tests, purity testing, immunogenicity testing, Enzyme-Linked ImmunoSpot assays (ELISPOT), sterility testing, pluripotency testing, cell viability testing, molecular integrity testing, concentration measurement, cell counting, composition testing.

8.4 Validation execution

8.4.1 General

The validation work shall be executed by trained and competent personnel, using the approved validation plan. Critical equipment for the processing method shall be qualified by installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

Validation needs to be readdressed, if periodic monitoring procedures (see Clause 11) have not fulfilled the acceptance criteria and investigation on non-conforming biological materials did not provide plausible explanation.

8.4.2 Validation site

Validation work that concerns a processing method shall be performed in the premises of the biobank laboratory. Validation work for a processing method that has been planned to be performed off-site biobank, shall take place at this off-site location. Work that concerns tests on the output biological materials, that can be necessary, shall be performed either by the biobank laboratory itself or by an external provider.

Results from validation studies, performed by suppliers or by peers and published in either application notes or scientific publications can be used as contributing validation evidence.

8.4.3 In-house or outsourced testing

8.4.3.1 In the context of the validation of a processing method, tests needed to be performed on the biological material(s) (e.g. viability, purity, pluripotency, molecular integrity, concentration, composition, growth capacity etc.) shall either be performed in-house or outsourced.

8.4.3.2 If testing is performed by the biobank laboratory itself, testing can be carried out according to ISO/IEC 17025. When conformity assessment is impractical, the biobank laboratory should utilize approaches that provide objective evidence for comparability of measurements, where such approaches are available and appropriate. This can include relevant external quality assessment or proficiency testing programs or the biobank can develop its own approaches.

8.4.3.3 The biobank shall have policies and use documented procedures to select competent external providers to perform specific tests of the biological materials, as part of the processing method validation. The biobank shall establish and maintain procedures to ensure that all tasks performed by external providers comply with specifications set by the biobank for such tasks. Evidence of the external provider's competence in the performed tests shall be established and records of its competence maintained.

This can be done by different means. Testing can be carried out according to ISO/IEC 17025 (or other relevant standards). When conformity assessment is impractical, evidence of external providers successfully participating in a relevant proficiency testing scheme and producing acceptable results on well-characterized materials of similar or equivalent nature to that of the biological material to be tested can also be considered appropriate. The external provider shall have documented procedures and evidence of competent staff. The external provider shall have validated the testing method(s). In cases where the competence of external providers, providing testing services, cannot be ascertained via provision of documentary evidence, the biobank should assess the competence of the external provider on-site or supervise on-site the operations carried out by the external provider.

8.4.3.4 The biobank shall ensure that all details of the methodology, the results and the descriptions of analytical protocols applied by any external provider are available. Suitable details of methodology shall be maintained by the biobank to allow the technical assessment of data.

8.5 Targets for processing method validation

8.5.1 General

Validation shall be performed on the previously implemented and optimized method that has been released for validation.

8.5.2 Fitness for purpose

8.5.2.1 For the validation of the fitness for purpose of a processing method, an operator shall process different biological materials, from different biological entities, collections or sampling events.

NOTE Examples are DNA extraction from blood from different donors, or DNA extraction from seeds from different plants, or culture of bacteria or fungi of different strains.

8.5.2.2 The feasibility and performance of intended analytical or other uses shall be verified using predefined acceptance criteria, taking into account specific properties of interest of the biological material that are known to influence its fitness for purpose. These properties of interest shall be measured and compared to the predefined acceptance criteria to demonstrate the fitness for purpose for the intended uses.

NOTE Examples of predefined acceptance criteria are yield, purity, viability above certain levels.

8.5.3 Reproducibility

For the purpose of the validation of the reproducibility of a processing method, multiple biological materials, of the same type, from the same biological entity or collection site (intra-donor or intra-collection reproducibility), can be processed by the same or different operators. If different operators are involved, the biobank shall assess inter-operator reproducibility of the method. Alternatively, different biological materials, of the same type, from multiple different biological entities or collection sites (inter-donor or inter-collection reproducibility), shall be processed by the same operator.

An experimental block design can be applied to assess the total reproducibility of the method (variation due to different collection sites, different operators, different batches of reagents, different equipment units, other critical factors).

The coefficient of variation (CV %) of quantitative properties, such as yield, purity, integrity shall be calculated and compared to predefined acceptance criteria. Qualitative properties can be assessed as well for their consistent (identical) outcome.

8.5.4 Robustness

8.5.4.1 Those experimental factors which are the most susceptible to variation during everyday processing, or which are known or suspected to impact the outcome of the processing method (critical factors) shall be varied in order to assess their impact (e.g. deviations in time, temperature). The degree of stress shall be defined and documented in the validation plan and generally corresponds to stress intensity that can be reached during everyday life (risk-based approach). The same biological material shall be used during this test. Pooled biological materials can also be used.

Acceptance criteria in robustness testing are either:

a) non-statistically-significant differences (at a predefined level of statistical significance) between baseline and stress condition results; or

b) differences not exceeding a predefined acceptance threshold, considered as technically significant threshold.

Appropriate statistical tests, for comparisons between groups, shall be used (e.g. analysis of variance (ANOVA) for single "latent" variable, principal component analysis (PCA) for linear combination of variables).

8.5.4.2 Validation of the robustness can include the robustness of the biological material to collection or transport condition variations (e.g. different anticoagulants, different transport temperatures, different times of transport) and/or to preparation condition variations (e.g. different enzymatic digestion times, different homogenization settings). When it is impractical for the biobank laboratory, part of this validation of robustness can be performed by an external provider (e.g. biological material collector/depositor).

8.5.4.3 The critical factors shall be documented and further considered for the annotation of each biological material undergoing processing. For simple processing methods, such annotation can be the Standard PREanalytical Code (SPREC)[28].

8.5.5 Homogeneity

If relevant, the biobank laboratory shall carry out an assessment of the homogeneity of a biological material in its final form.

Assessment of homogeneity can include the use of prior evidence (including prior experimental evidence), the conduct of an experimental homogeneity study on different aliquots or both. In most cases an experimental study is necessary.

NOTE Guidance on the implementation of homogeneity studies is provided in ISO Guide 35.

Many biological materials (e.g. solid human tissue) have inherent cellular heterogeneity. Therefore, if such biological material is the output of a processing method, assessment of homogeneity is not always relevant, and qualitative properties may only be used for assessment of homogeneity.

8.5.6 Stability

8.5.6.1 The results of stability studies performed in equivalent conditions by peers and published in peer reviewed scientific articles can be used as evidence of stability.

8.5.6.2 In the absence of such evidence, assessment of stability is required to establish that the degree of stability of the biological material is fit for purpose.

8.5.6.3 Testing performed for the assessment of stability can be carried out in compliance with ISO/IEC 17025. Stability testing can be performed only if sufficient homogeneity is demonstrated.

NOTE Guidance on the implementation of stability studies is provided in ISO Guide 35.

8.5.6.4 The properties of interest of the biological material shall be assessed for the adopted storage conditions. Effects of, e.g. light, moisture and temperature shall be assessed as a function of time for estimating a "shelf life" of the biological material.

8.5.6.5 When feasible, at least two representative portions from each type of biological material that is processed with the method shall be prepared, in sufficient quantities, for long term storage of multiple aliquots (in the same conditions, e.g. container type/storage temperature). The biological materials used for assessment of stability should be materials reserved for this activity. Their aliquots shall be used for assessment of long-term stability of the biological materials, prepared by the processing method, and they shall be tested for specific measurands/properties of interest at regular intervals, starting at the baseline values. Pooled biological materials can be used. Different storage temperatures can be used. Real

time stability testing should be preferred to accelerate stability studies. In case of accelerated stability study, real time testing should also be performed.

Stability shall be assessed both for:

a) statistical significance at a predefined level (e.g., ANOVA); and

b) technical significance (relative to predefined method-specific acceptable instability).

Statistically significant instability does not always correspond to technical instability. Technical instability shall be defined according to the required fitness for purpose and the requirements of the intended use; e.g. it can correspond to a predefined percent deviation from the baseline values. For qualitative properties, appropriate thresholds shall be defined. Where possible an indication of expiry date should be provided to the user of the biological materials, based on the results of stability studies.

8.5.6.6 The stability of the biological material under transport conditions shall also be assessed, if necessary.

8.6 Review and approval of validation report

8.6.1 The output of the processing method validation shall be a processing method validation report. This report shall be reviewed and approved by the biobank quality manager and the method shall be declared "validated" from the date of the signature of the report.

8.6.2 In case the current version of the SOP of the processing method has to undergo modifications, based on the conclusions of the validation report, a new validated version is put into production.

8.6.3 In case acceptance criteria are not met during initial validation, the biobank laboratory can decide to either modify the corresponding SOP and restart validation or repeat the formal validation procedure, or – in case of conflicting results – decide to maintain the corresponding SOP and limit its scope of application. All records related to the "failed" validation shall be retained. Any deviation from the SOP or the validation plan shall be documented in the validation report.

9 Further validation

9.1 Further validation of a validated processing method is required to address the effects of variation in parameters, such as changes in reagents or equipment, which are characterized as critical by the biobank laboratory, changes in the types of biological materials being processed, or changes in SOPs.

The need of revalidation, in whole or in part, shall be assessed based on change control procedures.

9.2 The method validation report shall be amended every time there is a new development or adaptation of the method (including results of stability testing).

10 Method verification

10.1 Standard processing methods, used without modification, shall be subject to verification by the biobank laboratory before being introduced into routine use.

Verification of a processing method is the procedure by which the biobank laboratory shows with documented evidence that specified requirements are met (e.g. manufacturer claims relative to a yield, concentration, purity of the output biological materials) and critical sources of variation in the performance of the processing method are considered.

10.2 A verification plan shall be documented, reviewed and approved by competent personnel and should contain:

a) the scope of the method;

b) the externally provided performance characteristics and the requirements for the method;

c) the critical parameters;

d) list of the trained/competent staff;

e) the activities that are planned to verify the performance characteristics (e.g. inspection, document review, customer feedback, or calculation).

10.3 Verification work shall be performed by trained and competent personnel of the biobank.

10.4 The output of the method verification shall be a statement of compliance that the method met the predefined requirements. The biobank shall maintain the results of the verification activities and any documentation relevant to the evidence of compliance with the requirements.

10.5 If a method does not comply with the requirements, actions shall be taken in order to achieve the compliance. All records related to verification shall be retained.

10.6 The biobank shall ensure ongoing monitoring according to Clause 11.

11 Ongoing monitoring of a processing method

11.1 General

11.1.1 Ongoing monitoring of a processing method requires assessment of the quality of the biological materials that have been the output of the method over a period of time. Such monitoring requires observation of a qualitative property (e.g. growing bacteria) or measurement of relevant properties of interest of the biological materials that are the output of the method (e.g. DNA yield, DNA purity).

11.1.2 Feedback data from biological material recipients/customers can also be used.

11.1.3 Feedback data shall be assessed with respect to the performance of the processing method.

11.2 Frequency of the monitoring

11.2.1 Assessment of the quality of the biological materials that are the output of the processing methods can be performed either by:

a) Systematic monitoring:

— on all biological materials upon their processing and before storage; and/or

— on all biological materials upon their distribution to customers.

b) Periodic monitoring:

— periodically on a predefined number of biological materials, with a predefined periodicity.

11.2.2 The type of monitoring and its frequency, where applicable, shall be defined according to the specific "biological material type/property of interest" combinations.

11.2.3 "For cause monitoring" shall take place in case of client claims, major changes to the processing method or internally detected non-conformities, which introduce doubt on the method's performance. In this case, targeted measurements shall be applied to the biological materials produced by the processing method concerned.

11.3 Planning

A monitoring plan shall be established and maintained to define the applicable monitoring approach according to 11.2, for each processing method. It shall also contain the assays to be applied for the monitoring, the biological materials to be tested, and the responsible person for testing as well as the time-period which is covered, i.e. the timespan, over which the processing method was used. The plan shall be reviewed and approved by competent personnel.

It is recommended to prepare an annual monitoring plan, covering all processing methods applied in the previous year.

11.4 Procedure of the systematic monitoring

11.4.1 The systematic monitoring is based upon control charts. Trend analysis, using results from measurements on processed biological materials, obtained over a defined period of time shall be performed. The control charts include the robust mean and standard deviation for each biological material type/property of interest combination. Acceptance criteria and criteria for detection of anomalies or trends shall be defined (e.g. Westgard rules, or rules based on fitness for purpose). Pareto charts can also be applicable in some cases. Every new measurement is then assessed against the defined acceptance criteria of the chart. If an anomaly is detected, an investigation shall be performed.

11.4.2 These trend analyses shall be performed at regular intervals. In case of changes in the processing method (or in the testing method, which is applied for the monitoring of the processing method) which have known or potential impact on the results, re-establishment of baseline statistics with definition of updated acceptance criteria is required.

11.4.3 In-process quality control materials can be used for the purposes of systematic monitoring. In this case, control charts for the measurements obtained on the in-process quality control material shall be used. The use of in-process quality control materials is indicated in the case of complex processing methods in which there is high variability between different input biological materials.

11.4.4 Records about the establishment of the baseline statistics and the definition of acceptance criteria shall be retained.

11.4.5 Records of monitoring checks based upon the control charts shall be retained.

11.5 Procedure of the periodic monitoring

11.5.1 For the periodic monitoring, different strategies for defining the biological materials to be tested can be applied:

a) either a number of randomly selected biological materials, prepared during a certain timespan, using the processing method to be assessed, is tested specifically for the periodic monitoring purpose;

b) or, for methods, where either the number of biological materials is too low or the testing method is destructive, and testing results are available from assays performed in a different context and in the targeted time-span (e.g. in the context of biological material distribution to customers), these results can be transcribed in the monitoring context ("retrospective, documentary monitoring").

11.5.2 If biological materials are selected randomly for monitoring purposes, the randomization procedure shall be documented.

11.6 External quality assessments (EQA)/Interlaboratory exercises

In addition to the internal monitoring activities, the biobank laboratory should participate in EQA/inter[1)]-laboratory exercise programs corresponding to its processing methods.

12 Record keeping and archiving

Detailed records, including raw data, of all validations shall be retained for a predefined period of time.

1) This also applies to multiple laboratories belonging to the same legal entity.

Annex A
(informative)

Processing and testing methods

Figure A.1 shows the distinction between processing and testing methods. The output of a processing method is a biological material which can undergo testing at some time point. The dashed rectangular area of the figure shows the scope of general requirements for the validation and verification of biological material processing methods in biobank laboratories.

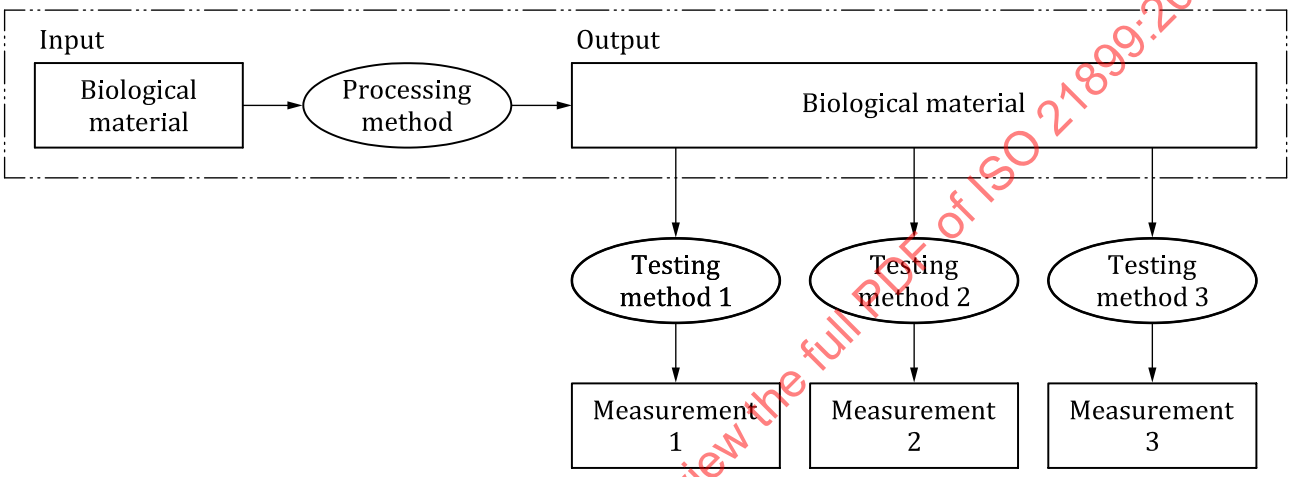

Figure A.1 — Distinction between processing and test methods