INTERNATIONAL STANDARD

ISO 20166-4

First edition
2021-07

Molecular in vitro diagnostic examinations — Specifications for preexamination processes for formalin-fixed and paraffin-embedded (FFPE) tissue —

Part 4: In situ detection techniques

Analyses de diagnostic moléculaire in vitro — Spécifications relatives aux processus préanalytiques pour les tissus fixés au formol et inclus en paraffine (FFPE) —

Partie 4: Techniques de détection in situ

Reference number
ISO 20166-4:2021(E)

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Published in Switzerland

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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).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

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 212, *Clinical laboratory testing and in vitro diagnostic test systems*.

A list of all parts in the ISO 20166 series can be found on the ISO website.

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.

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Introduction

Molecular in vitro diagnostics, including molecular pathology, has enabled significant progress in medicine. Further progress is expected by new technologies analyzing tissue morphology and biomolecules, such as (e.g. proteins, DNA, RNA and/or metabolites (e.g. glucose) in human tissues and body fluids.

In pathology, the majority of diagnoses are based on in situ staining of formalin-fixed and paraffin-embedded (FFPE) tissue sections. In the context of personalized medicine, classical histological staining (e.g. hematoxylin and eosin) for morphological evaluation is increasingly complemented by additional in situ detection techniques, such as immunohistochemistry or in situ hybridization, as well as molecular analysis of isolated biomolecules. For example, many regulatory bodies approved companion diagnostics in oncology are based on in situ detection techniques applied on FFPE tissue sections. Developments in personalized medicine and new technologies, such as multi-label immunostaining and computer-based analysis of digital images (e.g. generated by using a slide scanner) pose new requirements on standardization of pre-analytical procedures to obtain reproducible qualitative and quantitative results.

Profiles and/or integrity of biomolecules and their in situ localization, amount and accessibility for in situ detection in tissues can change drastically during the pre-examination process comprising specimen collection, tissue processing, embedding, transport, storage, sectioning and pretreatment for in situ detection. This makes the outcome from in situ detection in diagnostics or research unreliable or even impossible because the subsequent examination will not represent the in vivo state of molecules, but instead, an artificial profile or morphology generated during the pre-examination process.

Therefore, a standardization of the entire pre-examination process of FFPE tissue specimens intended for in situ examinations of morphology and biomolecules on FFPE tissue sections by using different in situ detection techniques, is needed.

There is multiple scientific evidence that several factors of the pre-examination phase influence the outcome (e.g. quality or quantity in terms of specificity or sensitivity) of in situ detection and, thus, can have major impact on the diagnostic results.

This document draws upon such work to organize and standardize the steps for formalin-fixed and paraffin-embedded (FFPE) tissue with regard to various in situ detection techniques in what is referred to as the pre-examination phase. This document is for the pre-examination phase of in situ detection techniques and is applicable to the whole spectrum of in situ detection techniques.

These include but are not limited to:

— Classical histological staining, e.g. Hematoxylin & Eosin staining (H&E);

— Histochemical techniques, e.g. Lipid staining, Periodic Acid Schiff (PAS) reaction, Perls' Prussian Blue reaction, Feulgen's reaction, enzyme histochemistry;

— Immunohistochemical staining (IHC) or immunofluorescence staining using antibodies (polyclonal, monoclonal or recombinant antibodies) or other affinity binders;

— Hybridization-based techniques such as RNA or DNA in situ hybridization (ISH) techniques, e.g. fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH), or silver enhanced in situ hybridization (SISH);

— Molecular analysis of isolated biomolecules that can be mapped to a defined region of an FFPE section (by e.g. in situ sequencing, imaging mass spectrometry).

In this document, the following verbal forms are used:

— "shall" indicates a requirement;

— "should" indicates a recommendation;

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— "may" indicates a permission;

— "can" indicates a possibility or a capability.

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Molecular in vitro diagnostic examinations — Specifications for preexamination processes for formalin-fixed and paraffin-embedded (FFPE) tissue —

Part 4: In situ detection techniques

1 Scope

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.

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 15189, *Medical laboratories — Requirements for quality and competence*

ISO 15190, *Medical laboratories — Requirements for safety*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 15189 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/

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3.1
affinity binder
molecules including affibodies, peptides, *antibody* (3.3) fragments or other small molecules that interact with *biomolecules* (3.6) and structures in a cell, and can be used in *in situ detection* (3.27) techniques

3.2
ambient temperature
unregulated temperature of the surrounding air

[SOURCE: ISO 20166-1:2018, 3.2]

3.3
antibody
protein (3.36) (immunoglobulin) produced and secreted by B lymphocytes in response to a molecule recognized as foreign (*antigen* (3.4)) and which is capable of binding to that specific *antigen* (3.4)

[SOURCE: ISO 16577:2016, 3.10, modified — "Note 1 to entry" has been deleted.]

3.4
antigen
substance that stimulates the production of *antibodies* (3.3) and reacts with them

[SOURCE: ISO 15089:2000, 3.5]

3.5
antigen retrieval
epitope retrieval
procedure(s) to unmask *antigens* (3.4)/*epitopes* (3.14) and restore their binding properties for *antibodies* (3.3) used in *immunohistochemistry* (3.25) by neutralizing the modifications introduced by *formalin fixation* (3.19), *tissue processing* (3.47) and *paraffin embedding* (3.33) of tissue

3.6
biomolecule
organic molecule produced in living organisms that is involved in the maintenance and metabolic processes of organisms

Note 1 to entry: The examples of organic molecule are *protein* (3.37), carbohydrate, lipid, or nucleic acid.

3.7
clearing
process step in *tissue processing* (3.47) in which formalin-fixed tissue is transferred from *dehydration* (3.10) reagent to clearing agent (for example, xylene) to prepare the tissue for *impregnation* (3.26)

3.8
cold ischemia
condition after removal of the tissue from the body until its stabilization or fixation

[SOURCE: ISO 20166-1:2018, 3.5]

3.9
decalcification
technique using chemical agents for removal of mineral (inorganic calcium) from bone or other calcified tissue to adjust the hard tissue components to the softness of *paraffin* (3.32) for sectioning

3.10
dehydration
process step in *tissue processing* (3.47) for removal of water from formalin-fixed tissue by immersing the tissue in a series of dehydrating reagent solutions of increasing concentration finishing with water free (100 %) solution

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3.11
deviation
departure from an approved instruction, procedure and/or method

[SOURCE: ISO 15378:2017, 3.7.5 modified — "approved (3.7.1) standard operating procedure (SOP) (3.7.10)" replaced by "approved instruction, procedure and/or method".]

3.12
diagnosis
identification of a health or disease state from its signs and/or symptoms, where the diagnostic process can involve *examinations* (3.15) and tests for classification of an individual's condition into separate and distinct categories or subclasses that allow medical decisions about treatment and prognosis to be made

[SOURCE: ISO 20166-1:2018, 3.7]

3.13
DNA
deoxyribonucleic acid
polymer of deoxyribonucleotides occurring in a double-stranded (dsDNA) or single-stranded (ssDNA) form

[SOURCE: ISO 22174:2005, 3.1.2]

3.14
epitope
antibody (3.3) binding site on a *biomolecule* (3.6) that is an *antigen* (3.4)

3.15
examination
analytical test
set of operations with the objective of determining the value or characteristics of a property

Note 1 to entry: Processes that start with the *in situ detection* (3.27) using *antibodies* (3.3), nucleic acid probes or dyes and include all kinds of parameter testing or chemical manipulation for quantitative or qualitative examination.

[SOURCE: ISO 15189:2012, 3.7, modified — Notes to entry 1 to 3 have been removed, Note 1 to entry has been added and "analytical test" has been added as a preferred term.]

3.16
examination manufacturer
analytical test manufacturer
entity that manufactures and/or produces the specific *analytical test* (3.15)

3.17
FFPE tissue
formalin-fixed, paraffin-embedded tissue
tissue *specimens* (3.42)/*samples* (3.41) having undergone fixation in *formalin* (3.18, 3.19), *tissue processing* (3.47), and *paraffin embedding* (3.33) in a tissue cassette

3.18
formalin
saturated aqueous formaldehyde solution which at 100 % contains 37 % formaldehyde by mass (corresponding to 40 % by volume)

[SOURCE: ISO 20166-1:2018, 3.11]

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3.19
formalin fixation
treatment of a *sample* (3.41) with *standard buffered formalin solution* (3.45) for stabilization

[SOURCE: ISO 20166-1:2018, 3.12]

3.20
formalin pigment
acid formalin haematin pigment acid
hematin
black to brown amorphous to microcrystalline granules representing an artefact in histologic sections prepared from tissues fixed in *formalin* (3.18, 3.19) having an increased formic acid concentration, which is produced by acid acting upon haemoglobin

3.21
grossing
gross examination
inspection of pathology *specimens* (3.42) with the bare eye to obtain diagnostic information, while being processed for further microscopic *examination* (3.15)

[SOURCE: ISO 20166-1:2018, 3.13]

3.22
histochemical technique(s)
in situ detection (3.27) technique(s) for the visualization and characterization of *biomolecules* (3.6) that involves chemical reactions with specific groups, radicals, or chemical bonds in *biomolecules* (3.6) and provide(s) information on the *biomolecules'* (3.6) in situ localization in *tissue sections* (3.49)

Note 1 to entry: The examples of *biomolecules* (3.6) are carbohydrates, lipids, other metabolites, *proteins* (3.36), amino acids, nucleic acids, pigments, or enzymes etc.

3.23
histological staining
in situ detection (3.27) technique undertaken to prepare *tissue sections* (3.49) by using histological stains (e.g. Haematoxylin-Eosin (HE), Chromotrop-Anilinblue (CAB)) to highlight features of the *tissue section* (3.49) and enhance *tissue section* (3.49) contrast

3.24
homogeneous
uniform in structure and composition

[SOURCE: ISO 20166-1:2018, 3.31]

3.25
immunohistochemistry
IHC
in situ detection (3.27) technique that uses the principle of *antibodies* (3.3) binding specifically to *antigens* (3.4) / *epitopes* (3.14) in biological tissues or cells to visualize *antigens* (3.4) (e.g. *proteins* (3.36)) using brightfield microscopy

3.26
impregnation
impregnation with paraffin
process step in *tissue processing* (3.47) for replacement of clearing agent and infiltration of tissue with molten *paraffin* (3.32)

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3.27
in situ detection
technique that allows for precise localization of a specific *biomolecule* (3.6) within a slide-mounted section

EXAMPLE *Immunohistochemistry* (3.25) for *protein* (3.36) detection, *in situ hybridization* (3.30) for nucleic acid detection, *histological staining* (3.23), *histochemical techniques* (3.22), MALDI imaging mass spectrometry, imaging mass cytometry, in situ Raman spectroscopy.

3.28
in situ detection system
detection system
set of reagents used to visualize the binding of molecules to their target in situ within a *tissue section* (3.49)

Note 1 to entry: Examples of molecules are *antibody* (3.3), *affinity binder* (3.1), and nucleic acid.

Note 2 to entry: Most common for *in situ detection* (3.27) are enzyme- and fluorophore-based detection systems.

3.29
in situ examination
analytical in situ test
examination (3.15) based on *in situ detection* (3.27)

3.30
in situ hybridization
ISH
in situ detection (3.27) technique that uses the principle of complementary nucleic acid probes binding specifically to segments of *RNA* (3.37) or *DNA* (3.13) in biological tissues or cells to visualize nucleic acids (e.g. *DNA* (3.13) or *RNA* (3.37)) using brightfield or fluorescence microscope

3.31
nonconformity
nonfulfillment of a requirement

[SOURCE: ISO 9000:2015, 3.6.9 modified — Note 1 removed.]

3.32
paraffin
paraffin wax
product obtained from distillates, consisting essentially of a mixture of saturated hydrocarbons, solid at *room temperatures* (3.40) used for *paraffin embedding* (3.33) of formalin-fixed tissue *specimens* (3.42)/*samples* (3.41)

3.33
paraffin embedding
embedding in paraffin
process following *tissue processing* (3.47) in which a tissue *sample* (3.41), is placed in melted *paraffin* (3.32) to achieve a hard surrounding matrix so that thin microscopic sections can be cut

3.34
post-translational modification
modifications on a *protein* (3.36), catalysed by enzymes, after its translation by ribosomes is complete that can be the addition of a functional group covalently to a *protein* (3.36) such as phosphorylation and neddylation, the proteolytic processing and/or folding processes necessary for a *protein* (3.36) to mature functionally

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3.35
pre-examination process
pre-analytical workflow
pre-analytical phase
pre-examination phase
process that starts, in chronological order, from the clinician's request and includes the *examination* (3.15) request, preparation and identification of the patient, collection of the *speciment(s)* (3.42), transportation to and within the medical laboratory, evaluation, *tissue processing* (3.47), *paraffin embedding* (3.33), FFPE block *storage* (3.46) and retrieval, sectioning (including mounting onto glass slides and drying), *storage* (3.46) of unstained slide-mounted *tissue sections* (3.49) (if applicable), and pre-treatment steps for *in situ detection* (3.27) techniques, and ends when the analytical *examination* (3.15) begins

Note 1 to entry: The pre-examination phase for *in situ detection* (3.27) includes preparative processes, e.g. *antigen/epitope retrieval* (3.5) and pre-hybridization procedures, which influence the outcome of the intended *examination* (3.15).

[SOURCE: ISO 15189:2012, 3.15, modified — An additional term was added, and more details were included.]

3.36
protein
type of biological *biomolecules* (3.6) composed of one or more chains with a defined sequence of amino acids connected through peptide bonds

[SOURCE: ISO 20166-2:2018, 3.14, modified – The terms "biological macromolecules" were replaced with "biological biomolecules"]

3.37
RNA
ribonucleic acid
polymer of ribonucleotides occurring in a double-stranded or single-stranded form

[SOURCE: ISO 20166-1:2018, 3.20]

3.38
RNA profile
amounts of the individual *RNA* (3.37) molecules that are present in a *sample* (3.41) and that can be measured in the absence of any losses, inhibition and interference

[SOURCE: ISO 20166-1:2018, 3.19]

3.39
RNase
ribonuclease
enzyme that catalyzes the degradation of *RNA* (3.37) into smaller components

[SOURCE: ISO 20166-1:2018, 3.21]

3.40
room temperature
for the purpose of this document, temperature in the range of 18 °C to 25 °C

Note 1 to entry: Local or national regulations can have different definitions.

[SOURCE: ISO 20166-1:2018, 3.22]

3.41
sample
one or more parts taken from a *specimen* (3.42)

[SOURCE: ISO 15189:2012, 3.24, modified — EXAMPLE has been removed.]

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3.42
specimen
primary sample
discrete portion of a body fluid, breath, hair or tissue taken for *examination* (3.15), study or analysis of one or more quantities or properties assumed to apply for the whole

[SOURCE: ISO 15189:2012, 3.16, modified — The term and definition is used here without the original notes.]

3.43
specimen container
container into which the tissue *specimen* (3.42) is transferred after its collection for further *pre-analytical workflow* (3.35) steps (e.g. transport and/or fixation)

3.44
stability
ability of a *sample* (3.41) material, when stored under specified conditions, to maintain a stated property value within specified limits for a specified period of time

Note 1 to entry: The analytes for the purpose of this document are *biomolecules* (3.6) located in situ/in the tissue.

[SOURCE: ISO 20166-1:2018, 3.24, modified — Note 1 to entry has been deleted and new Note 1 to entry has been added.]

3.45
standard buffered formalin solution
neutral buffered formalin
NBF
10 % *formalin* (3.18) solution in water with a mass fraction of 3,7 % (corresponding to a volume fraction of 4 %) formaldehyde, buffered to pH 6,8 to pH 7,2

Note 1 to entry: Standard buffered formalin solutions often contain small amounts of methanol to inhibit oxidation and polymerization of formaldehyde.

[SOURCE: ISO 20166-1:2018, 3.25]

3.46
storage
maintenance of biological material under appropriate conditions for intended use

3.47
tissue processing
process during the generation of *FFPE tissue* (3.17) consisting of the four consecutive steps tissue fixation, *dehydration* (3.10), *clearing* (3.7), and *impregnation with paraffin* (3.26)

3.48
tissue processor
automated instrument where tissue fixation, *dehydration* (3.10), *clearing* (3.7) and *impregnation (with paraffin)* (3.26) occur

[SOURCE: ISO 20166-1:2018, 3.27]

3.49
tissue section
very thin slice of tissue generated by cutting tissue with a dedicated section cutting device (i.e. microtome)

Note 1 to entry: *FFPE tissue* (3.17) is cut using a microtome to generate (µm-) thin sections that are mounted onto glass slides for performing *in situ detection* (3.27) techniques.

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3.50
validation
confirmation, throughout the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

Note 1 to entry: The word "validated" is used to designate the corresponding status.

[SOURCE: ISO 9000:2015, 3.8.13, modified — Notes to entry 1 and 3 have been removed.]

3.51
verification
confirmation, through provision of objective evidence, that specified requirements have been fulfilled

Note 1 to entry: The term "verified" is used to designate the corresponding status.

Note 2 to entry: Confirmation can comprise activities such as

— performing alternative calculations,

— comparing a new design specification with a similar proven design specification,

— undertaking tests and demonstrations, and

— reviewing documents prior to issue.

[SOURCE: ISO 9000:2015, 3.8.4]

3.52
warm ischemia
condition before the tissue is removed from the body, but deprived of its normal blood supply

Note 1 to entry: Disruption of normal blood supply varies significantly case by case. Therefore, warm ischemia duration and its effects depend on individual cases and it also can depend on the anatomy of the arterial blood supply.

[SOURCE: ISO 20166-1:2018, 3.29]

3.53
workflow
structured series of activities necessary to complete a task

[SOURCE: ISO 20166-1:2018, 3.30, modified - The word "structured" was added]

4 General considerations

For general statements on medical laboratory quality management systems and in particular on specimen collection, receipt, and handling (including avoidance of cross contaminations) see ISO 15189, ISO/IEC 17025 or ISO/IEC 17020. ISO/TS 20658 and ISO 20387 (for biobanking) can also apply. The requirements on laboratory equipment, reagents, and consumables according to ISO 15189 shall be followed; ISO/IEC 17025 and ISO/IEC 17020 can also apply.

All steps of the pre-examination, examination and post-examination processes (i.e. the entire workflow) can influence the diagnosis or research study results. Thus, this entire workflow shall be verified and validated. This includes specifically all pre-examination process steps such as the examination request, preparation and identification of the patient, collection of the primary sample(s), transportation to and within the medical laboratory, fixation, processing, embedding, sectioning and storage.

Pre-analytical workflow steps, which cannot always be controlled (e.g. duration and condition of warm ischemia depending on the surgical procedure), shall be documented. A risk assessment of pre-analytical

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