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Implants for surgery — Cleanliness of orthopedic implants — General requirements

Implants chirurgicaux — Propreté des implants orthopédiques — Exigences générales

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ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Fax: +41 22 749 09 47
Email: copyright@iso.org
Website: www.iso.org

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Foreword

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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 on 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 the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 150, *Implants for surgery.*

Introduction

Cleaning of orthopaedic implants is an essential step for achieving their biocompatibility as well as controlling the microbiological load required for their sterilization process.

Safe application of orthopaedic implants is related to their constitutive materials but also the contaminants that can be released from or reside on their surface. Cleanliness is a key factor to ensure the biocompatibility of an implant. When applicable, cleaning is an essential step to remove contaminations coming from the previous manufacturing steps. However, cleaning methods should not interact with materials and impair their biocompatibility or impair the performance of the implant. Moreover cleaning agents should be effectively removed unless it has been proven that they do not impair both the biocompatibility and the performance of the implant. As a consequence, the cleaning process validation is interconnected to the biological evaluation of the implant according to ISO 10993-1.

Orthopaedic implants can be delivered sterile or non-sterile. In both cases, it is the responsibility of the manufacturer to provide implants cleaned to remove manufacturing contaminants.

The objective of the cleaning validation is to verify the effectiveness of the cleaning process for reducing physical, chemical and microbial contaminants below a defined level. Evaluation and validation of cleaning methods is a difficult task that requires an exhaustive knowledge of the manufacturing process of the orthopaedic implants in order to identify potential contaminants and potential interactions between the cleaning process, the implant materials and the environment (e.g. the environment and handling of an implant following cleaning and subsequent packaging can influence the cleanliness of the implant).

As an alternative to final cleaning, the cleanliness of implants can be controlled by manufacturing in a clean environment and with clean processes. In this case, the cleaning of the implant before packaging might not be required but the cleanliness requirements defined in this document might apply.

Implants for surgery — Cleanliness of orthopedic implants — General requirements

1 Scope

This document specifies requirements for the cleanliness of orthopaedic implants, hereafter referred to as implants, and test methods for the cleaning process validation and controls, which are based on a risk management process.

This document does not specify requirements for packaging or sterilization which are covered by other International Standards.

This document applies to in-process cleaning and final cleaning.

This document does not apply to liquid or gaseous implants.

This document does not apply to cleaning processes performed by the user or under the responsibility of the user.

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 9377-2, *Water quality — Determination of hydrocarbon oil index — Part 2: Method using solvent extraction and gas chromatography*

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management system*

ISO 10993-5, *Biological evaluation of medical devices — Part 5: Tests for in vitro cytotoxicity*

ISO 11737-1, *Sterilization of medical devices — Microbiological methods — Part 1: Determination of a population of microorganisms on products*

ASTM D7066-04, *Standard Test Method for dimer/trimer of chlorotrifluoroethylene (S-316) Recoverable Oil and Grease and Nonpolar Material by Infrared Determination*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

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

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

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

3.1
cleaning
removal of *contaminants* (3.4) from an item to the extent necessary for further processing or for intended use

Note 1 to entry: *Contaminants* (3.4) present on the surface of an implant can be removed by mechanical, physical and/or chemical means. The ability of an implant to be cleaned can depend on many factors, especially: the chemical nature of the surface of the implant, the chemical nature of contaminants, the *cleaning process* (3.3), the design of the implants (for example, assembled surfaces, blind holes, small-diameter and long holes impair cleanability), morphology of the surface of the implant and porosities.

3.2
cleaning family
set of implants, cleaned with the same or an equivalent *cleaning process* (3.3), being less critical or comparably critical with respect to:

— the cleanliness specification of the *worst-case specimen(s)* (3.8), and

— the risks to be in a contaminated state when the cleaning process has been completed as that of the worst-case specimen(s)

3.3
cleaning process
set of technologies, including the required equipment and the defined sequence of cleaning steps (cleaning programs), the procedures (cleaning procedures, including handling), and the controls (cleaning controls)

3.4
contaminant
biological, chemical or physical substance on the implant that can impair the safety or the performance of the implant

3.5
final cleaning
cleaning (3.1) just before the implant is protected against further contamination before distribution

Note 1 to entry: For implants delivered sterile, the final cleaning is the cleaning just before the implant is protected against further contamination and sterilized by the manufacturer.

Note 2 to entry: For implants delivered non-sterile, the final cleaning is the cleaning just before the implant is protected against further contamination and delivered to the user, who will be responsible for sterilization.

3.6
in-process cleaning
cleaning (3.1) performed between two manufacturing steps in order to remove the contamination coming from previous manufacturing steps

Note 1 to entry: For example, if an implant is manufactured with the following steps: machining, cleaning 1, dimensional control, polishing, cleaning 2, laser marking, inspection, *final cleaning* (3.5), packaging in clean room and sterilization, then “cleaning 1” and “cleaning 2” are in-process cleanings.

Note 2 to entry: In-process cleaning is meant to include cleaning on raw materials or semi-finished products entering the manufacturing process.

3.7
critical in-process cleaning
in-process cleaning (3.6) defined to be essential for the final cleanliness of the implant

3.8
worst-case specimen
implant of a *cleaning family* (3.2) or test dummy/dummies, being representative of a cleaning family and having the highest risk to be in a contaminated state when the cleaning process has been completed, taking into account the nature and quantity of each type of *contaminant* (3.4) before cleaning and the ability of the implants of the family to be cleaned

Note 1 to entry: The nature and quantity of each type of *contaminant* (3.4) are typically related to production and cleaning processes.

Note 2 to entry: The ability of the implant to be cleaned is typically related to material(s), geometry and surface texture.

Note 3 to entry: Test dummies are manufactured with comparable processing method(s) and materials, and using the same installations and parameters for cleaning, packaging and sterilization (if applicable) that are used for the implants of the cleaning family.

Note 4 to entry: In the context of this document the term "worst-case specimen" always refers to cleaning, and should not be confused with worst-case specimen for other purposes (e.g. for sterilization).

3.9
cleanliness
state of an implant with levels of *contaminants* (3.4) below specified criteria

3.10
validation
documented procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications

[SOURCE: ISO/TS 11139:2006, 2.55]

3.11
exhaustive extraction
extraction, typically accomplished using multiple steps, that solubilizes the total amount of extractable substances present in a test article, as evidenced when the amount of extractables released in a subsequent extraction step is less than 10 % of the amount of extractables released in the first extraction step

4 General requirements

4.1 Quality management system

The activities described within this document shall be carried out within a formal quality management system.

NOTE One possible and widely used quality management system for medical devices is described in ISO 13485.

4.2 Risk management

Risk management is an iterative process that shall be conducted during the design and validation of the cleaning process and with ongoing use of the cleaning process.

NOTE One possible and widely used risk management system for medical devices is described in ISO 14971.

As part of the risk management, the cleaning process shall be evaluated for the measures that are necessary to achieve an intended level of cleanliness (e.g. production in a controlled environment or different methods of cleaning) and their integration in the sequence of manufacturing steps.

A cleaning process is included in the manufacturing process of an implant if hazards relating to possible contaminants, e.g. coming from the previous manufacturing steps, have been identified. As a consequence, design and validation of a cleaning process shall be conducted within a risk management system.

Hazards relating to cleaning shall be taken into account during the design of the cleaning process and when establishing design requirements for the critical in-process cleanings and the final cleaning (see 4.3). Annex A identifies some aspects of the cleaning process that can be considered to be sources of harm.

Risk assessment of hazards relating to cleaning shall be performed after designing the cleaning process (see 4.3) and shall take into account implant characteristics, manufacturing steps before cleaning, cleaning process characteristics, and the environment implemented after final cleaning. Cleanliness requirements shall be defined (see Clause 5) taking into account the contaminants which are intended to be removed by any in-process or final cleaning as well as additional contaminants introduced by the cleaning process itself.

At least the following questions shall be addressed during a risk assessment:

a) What are the potential contaminants in contact with the implants during the manufacturing steps preceding each critical in-process cleaning or final cleaning?

b) What are the risks associated to these contaminants?

c) What are the potential interactions between the contaminants and the implant material?

d) Are there previous critical in-process cleaning or other operations for removing these potential contaminants from the surface?

e) What are the potential contaminants brought by the cleaning steps?

It is acknowledged that there is no set of questions which covers every implant. This list is not exhaustive and additional questions might need to be addressed during risk assessment.

Based on the results of risk assessment at least the following additional questions shall be addressed:

f) Are the test methods selected for the validation of the cleaning process able to assess the level of the potential contaminants to be limited on the implants, taking into account the detection limit, quantitation limit and accuracy of the method?

g) What are the acceptance criteria for each cleaning family?

h) Following validation, what process control requirements are required to maintain cleanliness during manufacturing?

i) What process changes would require revalidation of product cleaning effectiveness?

Before assessing the performances of a critical in-process cleaning process or a final cleaning process, possible contaminants shall be identified, appropriate test methods shall be determined and acceptance criteria shall be established as part of a risk management process.

Based on cleanliness acceptance criteria (see Clause 5) cleaning validation can be performed (see 4.4).

Figure B.1 illustrates the relation between cleaning design, validation and risk management.

4.3 Design of cleaning process

The design requirements for the critical in-process cleanings and the final cleaning shall be defined, based on implant characteristics, the intended performance of the implant as well as manufacturing steps before cleaning and an analysis of the hazards being introduced by the cleaning process itself (see Annex A). The cleaning processes shall be designed in order to reach the cleanliness acceptance criteria of the implant after final cleaning addressed in Clause 5.

The manufacturer, in cooperation with the cleaning subcontractor if applicable, shall define which cleanings are critical in-process cleanings and which is a final cleaning, based on a risk analysis of the manufacturing process and the influence of the in-process cleaning step on the final cleanliness of the implant. The risk assessment shall be used to determine sequence of events that have the highest probability of occurrence and/or severity. Subsequent activities in the design, verification and validation of the product and processes (including inspection steps) should then concentrate on the development of control measures to mitigate these risks.

If a drying operation is performed at the end of the cleaning, drying shall be considered to be part of the cleaning.

The cleaning process shall be designed in such a way to not degrade the biocompatibility and the intended performance of the implant.

The cleaning process shall be designed in order to limit contamination of the implant with cleaning agents, rinsing agents or contaminants coming from the cleaning process itself.

The cleaning process shall be able to decrease the contaminations coming from the previous manufacturing steps to an adequate predetermined level.

For final cleaning of implants, in order to prevent contamination of implants after cleaning, an adequate controlled environment or protection shall be implemented between final cleaning and packaging.

NOTE 1 Controlled environment does not necessarily mean the use of a clean room. While clean rooms are usually used for implants delivered sterile, this might not be the case for implants delivered non-sterile.

NOTE 2 ISO 14644 (all parts) contains information which might be useful, if cleanrooms and associated controlled environments are used.

The manufacturer may choose to define cleaning families in order to simplify validation or continued process verification activities of the cleaning process. In this case, criteria for defining the cleaning families shall be justified and documented. When determining if an implant is represented by the worst-case specimen for a cleaning family, the manufacturer shall take into account the cleanliness specifications, the ability of the implant to be cleaned as well as the equivalence of the cleaning process of the worst-case specimen and the cleaning process of the implant. For inclusion of a new implant into a cleaning family, it shall be ensured that it is represented by the worst-case specimen.

4.4 Validation

The critical in-process cleaning processes and the final cleaning process shall be validated in order to establish that the processes consistently yield implants complying with the cleanliness acceptance criteria defined for each critical in-process cleaning and acceptance criteria defined in accordance with Clause 5 for final cleaning.

NOTE 1 Cleaning processes and agents might influence the materials, surface properties, coatings or performance(s) of the implant.

NOTE 2 Guidance for validation of processes is given in IMDRF SG3-N99-10-2004.

The validation of the cleaning processes shall address at least the following, if applicable:

a) types of contamination to be removed as identified during the risk assessment (see 4.2);

b) implant characteristics:

   1) implant materials;

   2) implant shape and accessibility of its different surfaces to the cleaning agent;

c) cleaning steps:

   1) removing contaminations from the implant with cleaning agents;

2) removing cleaning agents with rinsing agents;

3) removing rinsing agents.

Validation shall be conducted on each implant or each cleaning family (see 4.3). Validation shall comprise tests at the relevant limits of the process, to demonstrate that even in worst case conditions, the cleanliness requirements (see Clause 5) can be fulfilled and that the process consistently yields product meeting its cleanliness acceptance criteria.

NOTE 3 In some cases the relevant limits of the process might be both the lower and upper limits, while in other cases only one of these limits might be relevant.

NOTE 4 ASTM F3127 provides guidance on cleaning process validation methods.

When using cleaning families, the worst-case specimen shall be used for conducting validation under the worst-case conditions as determined by the manufacturer or cleaning subcontractor, if applicable. When determining the worst-case conditions, each step (e.g. cleaning, rinsing, drying) of the cleaning process shall be taken into consideration. Based on the risk assessment, the manufacturer shall justify and document why any implant or test dummy is the worst case.

A risk assessment shall be performed after changes are made to the processing method, installations and/or parameters used for the manufacturing. The risk assessment shall determine if the cleaning process shall be revalidated and determine the extent of the revalidation. If the cleaning method, the cleanliness specifications or the worst-case specimen of a cleaning family are changed, the cleaning process shall be revalidated. Cleaning validation is interconnected with the biological evaluation and implant sterilization validation. Even if cleaning process validation gives a high level of confidence that risks relating to cleaning are acceptable, the acceptability and validation of the cleaning design is only possible after implant biological evaluation according to ISO 10993-1 and implant sterilization validation. If new hazards are identified during biological evaluation or implant sterilization validation which can be mitigated by the cleaning process, the impact of these new hazards on cleanliness acceptance criteria and cleaning validation shall be assessed. The order of cleaning validation, biological evaluation and implant sterilization validation depends on the strategy of the manufacturer. Cleaning validations are typically performed before or in parallel to biological evaluation and implant sterilization validation.

NOTE 5 A possible order for cleaning validation, biological evaluation and implants sterilization validation is given in Figure C.1.

NOTE 6 Cleanliness, microbiological contamination and biocompatibility of the implant might be influenced by the implant packaging.

Figure C.1 illustrates the relation between cleaning validation, biological evaluation and sterilization validation.

4.5 Sampling

A sampling plan with an appropriate number of samples shall be established as part of the risk assessment of the cleaning process. When appropriate (for example, when establishing the reproducibility of the process), sampling plans can be based upon statistically valid rationale for number of test specimens.

When validating the process in the worst case conditions, each worst-case condition shall be tested. When establishing the reproducibility of the process, at least 3 cleaning batches shall be tested.

4.6 Manufacturing of test specimens

In order to establish the conformity to the requirements of this document, tests shall be conducted on specimens manufactured, cleaned and packaged with methods, installations and in an environment representative of or more challenging than the manufacturing, cleaning and packaging process applied to the implant.

For the validation of critical in-process cleanings, packaging of specimens can be required between cleaning and testing of specimens, even if a packaging is not performed during the normal manufacturing at this stage. In this case, care shall be taken to ensure that the packaging does not influence the cleanliness of the specimens.

If a test (for example, cytotoxicity) requires that specimens be sterilized, the sterilization method shall be that applied for terminal sterilization (for implants delivered sterile) or recommended for sterilization by the user (for implants delivered non-sterile).

The processing method, installations and parameters used for the manufacturing, cleaning, packaging and sterilization (if applicable) of the test specimens shall be documented.

4.7 Testing methods

All the test methods used to demonstrate the conformity to the requirements of this document shall be validated and documented.

NOTE 1 Requirements for the competence of testing laboratories can be found in ISO/IEC 17025.

The following elements shall be documented, if applicable:

a) justification of the test method(s) used according to the types of contaminant that can be present on the implant;

b) extraction efficiency;

c) detection limit, quantitation limit and accuracy of the method;

d) extraction blanks and reference materials;

e) adequacy to demonstrate the conformity to the predetermined acceptance criteria.

NOTE 2 Methods for the validation of analytical procedures can be found in ICH Q2(R1).

5 Cleanliness evaluation: Test methods and cleanliness acceptance criteria after final cleaning

5.1 General

Subclauses 5.2 through 5.8 define tests to be considered when assessing the performance of each critical in-process cleaning and/or final cleaning. If adequately justified, some of the tests listed in 5.2 through 5.8 may be excluded based on the cleanliness requirements of the implant, the characteristics of the production and/or the cleaning process, the data gathered from previous cleaning processes and the data available from history.

Based on the type of contamination that can be present on the implant, other tests may be conducted. The preliminary cleanliness requirements shall be established by documenting the acceptance criteria for each test. Final cleanliness requirements shall be established after the results of the biological evaluation according to ISO 10993-1 and the results of the implant sterilization validation are available (see also 4.2 and 4.4).

NOTE 1 For the relation between production and/or cleaning design, validation and risk management, see Annex B.

NOTE 2 For the relation between cleaning validation, biological evaluation and sterilization validation, see Annex C.

5.2 Visual inspection

Acceptance criteria for visual inspection for visible contaminants remaining after cleaning shall be established by the manufacturer of the implant.

After cleaning, the implant being inspected shall comply with the manufacturer's acceptance criteria.

NOTE EN 13018 is one method that can be used for acceptance criteria for visual inspection.

5.3 Bioburden

If the purpose of the cleaning process is to ensure that the bioburden is less than or equal to a predetermined level, the bioburden on the implant shall be determined as specified in ISO 11737-1.

Specimens shall not be sterilized.

The predetermined level shall be sufficiently low such that the sterilization method specified is adequate to achieve the desired sterility assurance level.

The results shall be less than or equal to the predetermined level.

5.4 Bacterial endotoxins

If the purpose of the cleaning process is to reduce the bacterial endotoxin contamination, then a validated test shall be conducted to measure the level of bacterial endotoxins.

If an endotoxin limulus amebocyte lysate (LAL) test is used, it shall be conducted according to an established method described in a recognized Pharmacopoeia after extraction from the implant with a validated method. The level of bacterial endotoxin per implant shall be not more than 20,0 Endotoxin Units.

NOTE 1 Orthopaedic implants are not usually in contact with cerebrospinal fluid. In case of contact with cerebrospinal fluid, other limits can apply.

NOTE 2 AAMI ST72 gives helpful assistance for selection of test methods and acceptable levels of endotoxin contamination. It also gives helpful information on the effect of sterilization on endotoxin contamination.

NOTE 3 European Pharmacopoeia, Section 2.6.14 and USP, Section <85> present appropriate methods for LAL testing.

5.5 Organic contaminants

5.5.1 General

For chemical analysis of organic contaminants a number of methods can be considered as common practice. Each method possesses advantages and disadvantages and might not detect all organic contaminants possible in the production of orthopaedic implants and/or introduced by the cleaning process. Selection of the method(s) to be applied shall be based on, at least:

a) type of contamination that can be present on the implants (see 4.2 and 5.1);

b) type of implant material(s);

c) sensitivity of the analytical method.

The total organic carbon (TOC) method or another suitable method shall be used for detection of water-soluble organic contaminants.

The total hydrocarbons (THC) method or another suitable method shall be used for detection of hydrocarbons soluble in nonpolar solvents, unless there is no risk of contamination with hydrocarbons.

Requirements for extraction and detection for the TOC and THC methods are described in 5.5.2 and 5.5.3.

NOTE 1 Some implant intrinsic materials might release organic contaminants in the extraction solvent and it might be necessary to implement adequate procedures to differentiate between intrinsic materials of the implant and contaminants.

The tests may be conducted on either sterilized or non-sterilized specimens.

NOTE 2 Sterilization can have an influence on type and amount of organic contaminants resulting out of production and/or cleaning.

Biological evaluation data from devices with known organic contamination, manufactured with similar materials, manufacturing and cleaning processes may be used to establish preliminary or, if appropriate, final acceptance levels for organic contaminants.

NOTE 3 TOC and THC methods are able to detect a large spectrum of organic contaminants without the possibility of identification of specific contaminants. For the TOC method, water is used for extraction, which results in reduced exhaustiveness with respect to non-polar contaminants. Both methods are useful to demonstrate, during the cleaning validation, that the process is under control. They do not intend to demonstrate that specific organic contaminants are non-toxic or are non-critical with respect to biological effects. If a company has no historical data on TOC or THC tests that can be related to a corresponding biological evaluation, the limits set forth in NF S94-091 (0,500 mg per implant for TOC and 0,500 mg per implant for THC) can serve as a starting point for acceptance levels. Specific organic contaminants can already be critical in concentrations significantly below the limits given by NF S94-091. Both, type and amount of the single organic contaminants are relevant.

NOTE 4 One common approach is to first quantify the contamination. Subsequent identification of the contaminants can be helpful to understand the type of contamination (e.g. in case of untypically high contamination). However, the identification before quantification of contamination can be helpful to define allowable limits of contamination.

5.5.2 Extraction

Organic contamination shall be determined after exhaustive extraction from the implant using an appropriate solvent.

For water-soluble organic contaminants, water of sufficient purity not to interfere with the test method shall be used as a solvent.

For hydrocarbon contaminants, non-polar solvents are preferable for extraction and should be used. The solvent used for THC tests shall be chosen in order not to decompose the tested material and in order to avoid leaching from the material. If compatible with the material, hexane or halogenated solvents may be used. For example, for UHMWPE and PEEK implants propyl alcohol may also be used despite being a low-polar solvent.

Care shall be taken that the equipment to be used for extraction does not interfere with the solvent.

The extraction conditions shall be justified.

NOTE 1 Extraction methods can be found in ISO 10993-12, ASTM F2459 or ASTM G136.

The exhaustiveness of extraction shall be demonstrated.

NOTE 2 When the quantity extracted is below the quantification limit after the first extraction, it can be considered that exhaustiveness of extraction has been demonstrated.

The exhaustiveness of extraction conditions shall be verified on the worst-case specimen prior to finalizing testing on the cleaning family.

5.5.3 Detection

Detection including quantitation and/or identification of organic contamination as selected according to 5.1 and 5.5.1, shall be performed by validated methods.

The TOC, if investigated, shall be determined in the extracts and shall be quantified using such methods as described in EN 1484, European pharmacopeia 2.2.44, or USP <643>.

The THC, if investigated, shall be determined in the extracts and shall be quantified using methods such as gas chromatography as described in ISO 9377-2, Fourier Transform Infrared Spectroscopy (FT-IR) as described in ASTM D7066-04, or another validated test method.

5.6 Inorganic contaminants

The inorganic contaminants likely to be present on the implant shall be identified during the risk assessment as required in 4.2.

The inorganic contaminants identified to be critical in the risk assessment shall be determined after exhaustive extraction from the implant using water, water supplemented with acid, or another adequate solvent, if justified.

Care shall be taken that the equipment to be used for extraction does not interfere with the solvent.

The extraction conditions shall be justified.

NOTE 1 Extraction methods can be found in ISO 10993-12, ASTM F2459 or ASTM G136.

The exhaustiveness of extraction shall be demonstrated.

NOTE 2 When the quantity extracted is below the quantification limit after the first extraction, it can be considered that exhaustiveness of extraction has been demonstrated.

The exhaustiveness of extraction conditions shall be verified on the worst-case specimen prior to finalizing testing on the cleaning family.

NOTE 3 Some implant intrinsic materials might release inorganic contaminants in the extraction medium and it might be necessary to implement adequate procedures to differentiate between intrinsic materials of the implant and contaminants.

After extraction, a suitable method shall be used in order to assess inorganic contaminants. Examples of suitable methods are:

a) inductively coupled plasma in combination with atomic or optical emission spectrometry;

b) inductively coupled plasma in combination with mass spectrometry;

c) ionic chromatography;

d) ionic chromatography in combination with mass spectrometry.

NOTE 4 If water is used for extraction, the conductivity of the extract can be used to indicate soluble ionic species contamination before using more specific test methods.

The inorganic contaminant acceptance levels shall be determined using the data on the biological effects of each inorganic contaminant.

NOTE 5 A possible method for determining allowable limits for inorganic contaminants is provided in ISO 10993-17. Acceptance criteria for elemental impurities can also be found in ICH Q3D.

5.7 Particulate contamination

If the purpose is to demonstrate cleanliness regarding particulate contaminants, then corresponding investigations shall be conducted.

Selection of type and sensitivity of the test shall be performed based on the results of the risk management process. If extraction is conducted, care shall be taken to avoid particles produced as a result of mechanical forces applied during the extraction process.

NOTE AAMI TIR42 deals with the evaluation of particulates associated with vascular implants. However, AAMI TIR42:2010, Clause 8 and Annex A give helpful assistance for selection of acceptable levels and test methods of particulate contamination that could be applied to other types of implants.

5.8 Cytotoxicity

The cytotoxicity of the orthopaedic implant shall be determined using a method described in ISO 10993-5. The specimens shall be sterilized.

Any orthopaedic implant demonstrating a cytotoxic effect as defined in ISO 10993-5 shall be investigated to determine the cause of the cytotoxic effect. If this effect is related to contamination not removed by the cleaning process or to the cleaning process itself, control measures to mitigate this risk shall be implemented.

NOTE Cytotoxicity is usually part of the biological evaluation of the implant as per ISO 10993-1. It is a useful *in vitro* test, sensitive to many types of contaminants, which can be used to assess the effectiveness of the cleaning process. However, even if a cytotoxic effect is observed, this might not be related to the cleaning process and other root causes might have to be investigated.

6 Continued process verification

To ensure the fulfilment of defined cleanliness requirements, a routine monitoring of the critical process parameters and/or process environment, according to documented procedures, shall be implemented.

Routine control testing of the cleaning processes shall be established as part of the quality management system to document the type and time interval for each periodic test.

The frequency for performing each test shall be determined taking into account the reproducibility of the process, the risks related to any contaminants as well as the frequency and volume of manufacture.

7 Documentation

All documents and records required to demonstrate conformity to this document shall be established and maintained in a manner consistent with the requirements of the manufacturer's quality management system.

Annex A
(informative)

Potential sources of harm in a cleaning process

During the design of a cleaning process, at least the hazards relating to the following characteristics should be considered:

— shape of implants and accessibility of its different surfaces;

— constitutive material(s) of the implant;

— contamination of the implant before cleaning;

— physico-chemical characteristics of the implant;

— cleaning technology;

— cleaning equipment, fixtures, baskets and control systems;

— maintenance methods and frequency;

— cleaning agent used;

— concentration of the cleaning agent;

— purity and potential toxicity of the liquid agents, especially for the last cleaning or rinsing steps;

— action of the cleaning agent on bacteria and fungi;

— action of the cleaning agent on physicochemical contamination;

— cleaning temperature;

— mechanical effects during cleaning (ultrasound, agitation, and spraying);

— position of implants during cleaning, rinsing and drying;

— load of the cleaning unit;

— cleaning time;

— renewing of the cleaning agent;

— succession of the cleaning and rinsing steps;

— rinsing agent used;

— rinsing temperature;

— mechanical effects during rinsing;

— renewing of the rinsing agent;

— rinsing time, flow and volume;

— drying method;

— drying temperature;

— drying time;

— aeration, HEPA filtration, air locks, cascading air pressurization.

Annex B
(informative)

Relation between cleaning process design, validation and risk management

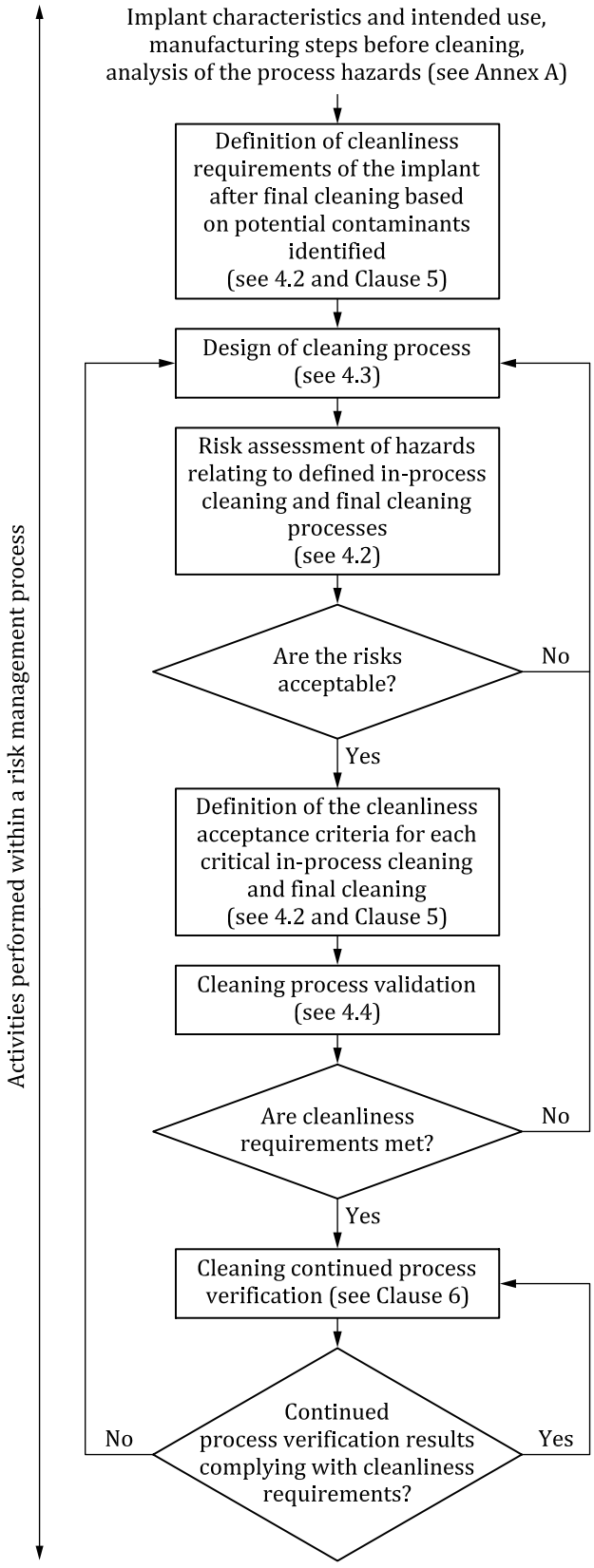

Figure B.1 — Design and validation of the cleaning process as part of the risk management

Annex C
(informative)

Relation between cleaning validation, biological evaluation and sterilization validation

In Figure C.1, it is proposed to perform the cleaning validation before biological evaluation and sterilization validation. Cleaning validation, biological evaluation and sterilization validation can also be performed in a different order but if the cleaning validation demonstrates that the cleaning process has to be modified, biological evaluation and sterilization validation are evaluated for any impact after implementation of the changes.

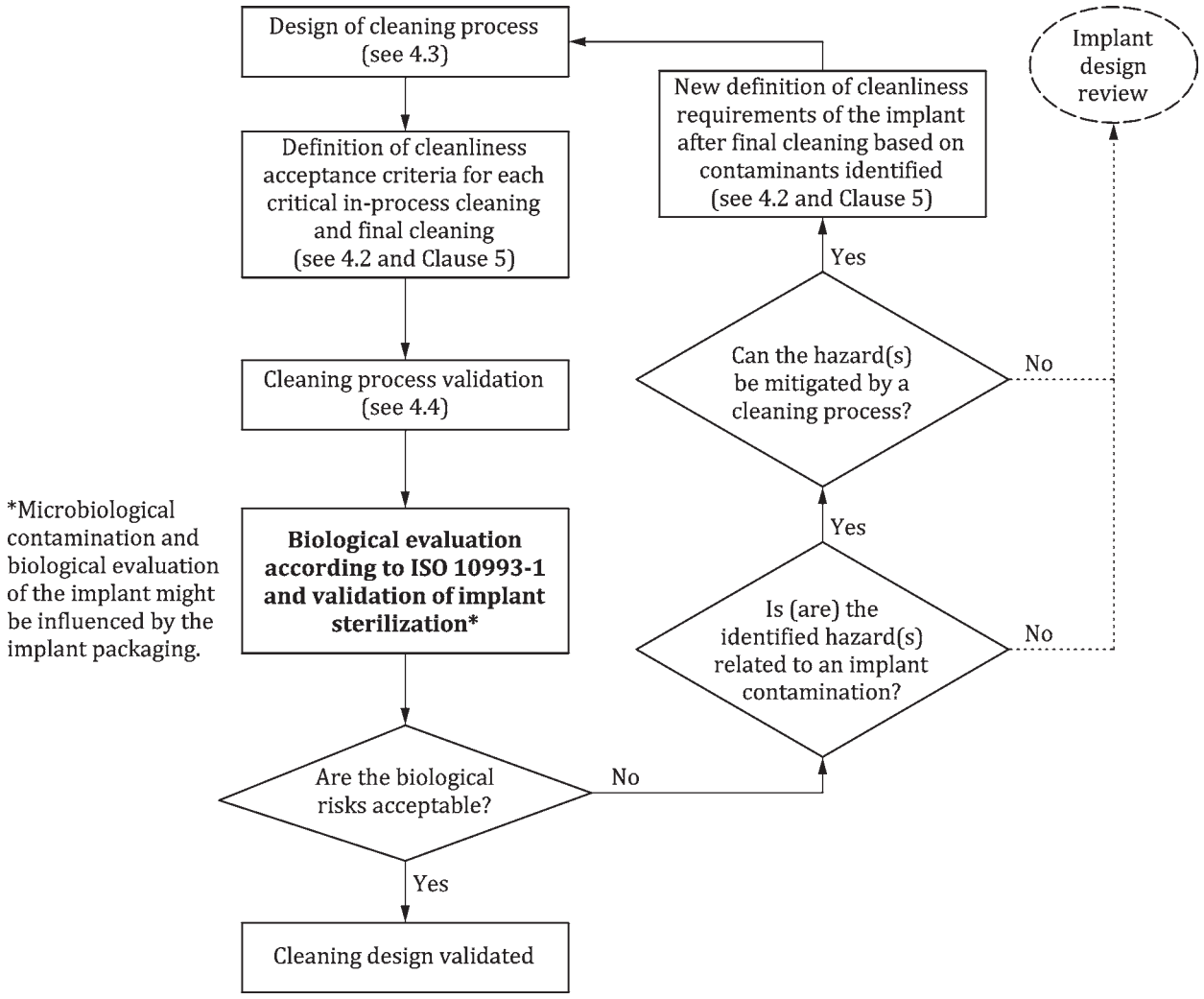

Figure C.1 — Relation between cleaning validation, biological evaluation and sterilization validation

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