INTERNATIONAL STANDARD

ISO 19227

First edition
2018-03

Implants for surgery — Cleanliness of orthopedic implants — General requirements

Implants chirurgicaux — Propreté des implants orthopédiques — Exigences générales

Reference number
ISO 19227:2018(E)

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Published in Switzerland

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Foreword

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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;