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Aseptic processing of health care products —

Part 7: Alternative processes for medical devices and combination products

Traitement aseptique des produits de santé —
Partie 7: Procédés alternatifs pour les dispositifs médicaux et les produits de combinaison

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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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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.

ISO 13408-7 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

ISO 13408 consists of the following parts, under the general title *Aseptic processing of health care products*:

— *Part 1: General requirements*

— *Part 2: Filtration*

— *Part 3: Lyophilization*

— *Part 4: Clean-in-place technologies*

— *Part 5: Sterilization in place*

— *Part 6: Isolator systems*

— *Part 7: Alternative processes for medical devices and combination products*

Introduction

ISO 13408 is the International Standard, published in a series of parts, for aseptic processing of health care products. Historically, sterile health care products that are aseptically produced have typically been liquids, powders or suspensions that cannot be terminally sterilized. More recently, medical devices and health care products have been developed that are combined with medicinal products, including biological and viable cells, that cannot be terminally sterilized.

The application of ISO 13408-1 to these medical devices and combination products can require the development of alternative approaches to process simulation. This part of ISO 13408 specifies requirements and provides guidance for developing such alternative approaches for the qualification of aseptic processes through process simulation of medical devices and combination products that meet the requirements of ISO 13408-1.

ISO 13408-1:2008, 10.1.2 permits the use of alternative process simulation approaches, based on particular medical devices or combination products, where the substitution in full with sterile liquid media might not be possible.

Medical devices and combination products that typically require aseptic processing might include, for example, the following.

a) Medical devices that cannot be terminally sterilized and where the process simulation approach according to ISO 13408-1 cannot be applied:

   — bioprostheses (e.g. heart valves, vascular implants);

   — biodegradable implants (e.g. hernia meshes);

   — artificial and/or non-viable biologically based matrixes;

   — extracorporeal processing devices (e.g. immuno-adsorbers);

   — implantable osmotic pumps;

   — hermetically sealed electromechanical devices and partially enclosed electronic devices (e.g. invasive and non-invasive diagnostic devices).

b) Combination products (including viable cell-based combination products):

   — implants coated with drug and/or biologically derived substances (e.g. drug-coated stents, carrier materials with protein, bone-graft material with growth factors, biodegradable drug-coated stents);

   — wound dressings (e.g. dressings with haemostatic agents, tissue sealants, or biologics);

   — transdermal or injectable delivery systems (e.g. drug-coated or biologics interstitial patches);

   — kits containing a biological or drug component (e.g. demineralized bone matrices).

For such products, a risk management strategy and method(s) can be used for the identification, evaluation and quantification (estimation) of contamination risks throughout the entire product/process life cycle. Environmental monitoring and microbiological studies can be performed on individual steps of the process to evaluate the effectiveness of contamination controls and risk mitigations. The design of the process simulation can then be driven by the results of the risk analysis. If the results of the process simulation are acceptable, this provides evidence that the aseptic process is in a state of contamination control (i.e. no extrinsic microbiological/microbial contamination has been introduced during the aseptic process).

This part of ISO 13408 should be read in conjunction with ISO 13408-1.

Within this International Standard, text that supplements ISO 13408-1 by providing additional requirements or guidance is identified by the prefix “Addition”.

Aseptic processing of health care products —

Part 7:
Alternative processes for medical devices and combination products

1 Scope

This part of ISO 13408 specifies requirements and provides guidance on alternative approaches to process simulations for the qualification of the aseptic processing of medical devices and combination products that cannot be terminally sterilized and where the process simulation approach according to ISO 13408-1 cannot be applied.

This part of ISO 13408 describes how risk assessment can be used during the development of an aseptic process to design a process simulation study for medical devices and combination products in those cases where a straightforward substitution of media for product during aseptic processing is not feasible or would not simulate the actual aseptic process.

2 Normative references

The following referenced documents are indispensable for the application 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 13408-1:2008, *Aseptic processing of health care products — Part 1: General requirements*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 13408-1 and the following apply.

3.1
extrinsic contamination
ingress of material of external origin during the manufacturing process

NOTE The focus of extrinsic contamination in this part of ISO 13408 is biological agents e.g. bacteria, mould, yeast.

3.2
process simulation
exercise that simulates the manufacturing process or portions of the process in order to demonstrate the capability of the aseptic process to prevent biological contamination

3.3
risk management
systematic application of quality management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk

[ISO 14971:2007, definition 2.22]

3.4
surrogate product
item designed to represent product in process simulations and which is comparable to the actual product

4 Quality system elements

ISO 13408-1:2008, Clause 4 applies.

5 Aseptic process definition

5.1 General

ISO 13408-1:2008, 5.1 applies.

5.2 Risk management

5.2.1 General

ISO 13408-1:2008, 5.2.1 applies with the following additional requirements.

a) Risk assessment shall consider all steps of the aseptic process and determine whether the aseptic process is to be simulated in one continuous process or divided into sub-processes for the purposes of process simulation.

Risk assessment shall not be used to justify the simulation of only some but not all of the processes of an aseptic process.

NOTE 1 Successful process simulation provides evidence of the capability of the specified aseptic process to produce an acceptable overall residual risk of microbiological/microbial contamination.

NOTE 2 The risk assessment method selected should be appropriate for the given stage of aseptic process development.

b) A comprehensive risk assessment process may not be required for the design of the process simulation in instances where the approach is readily discernable. The rationale for the decisions reached shall be documented.

5.2.2 Identification of microbiological contamination risks

ISO 13408-1:2008, 5.2.2 applies.

5.2.3 Assessment of contamination risks

ISO 13408-1:2008, 5.2.3 applies.

5.2.4 Monitoring and detection of contamination

ISO 13408-1:2008, 5.2.4 applies.

5.2.5 Prevention of contamination

ISO 13408-1:2008, 5.2.5 applies.

The following additional requirements to ISO 13408-1:2008, 5.2, concerning risk management, apply:

5.2.6 Use of risk assessment during the development and initial qualification of the aseptic process prior to commercial production

5.2.6.1 An acceptable level of contamination risk shall be defined. A risk assessment shall be performed during the development of the aseptic process. Risk control measures to prevent microbiological/microbial contamination for each step in the aseptic process shall be identified.

5.2.6.2 The estimation of contamination risk by quantitative methods and the verification of effectiveness of risk mitigation procedures shall be determined. Methods such as microbiological and particulate monitoring of the product, personnel and environment may be used.

NOTE Quantitative risk modelling can also be applied.

5.2.6.3 The outcome of the risk assessment shall be used in the design of the process simulation study.

5.2.6.4 Risk management shall be applied iteratively. The risk assessment shall be updated as necessary as the aseptic process develops and changes during development.

5.2.7 Use of risk assessment for the aseptic process simulation for process validation of commercial production

Risk assessment shall be used to design the process simulation for validation of the commercial aseptic process. Risk assessment shall identify those actions to be included in the process simulation and their appropriateness.

NOTE Annex A provides a practical application of risk management in designing a process simulation for a combination drug/device.

6 Manufacturing environment

ISO 13408-1:2008, Clause 6 applies.

7 Equipment

ISO 13408-1:2008, Clause 7 applies.

8 Personnel

ISO 13408-1:2008, Clause 8 applies.

9 Manufacture of the product

ISO 13408-1:2008, Clause 9 applies.

10 Process simulation

10.1 General

ISO 13408-1:2008, 10.1 applies.

10.2 Media selection and growth support

ISO 13408-1:2008, 10.2 applies.

10.3 Simulation procedures

ISO 13408-1:2008. 10.3.1 applies with the following additional requirements.

a) General considerations

The process simulation approach for a given medical device or combination product is based on a detailed knowledge of the entire aseptic process definition including discrete process steps and interventions as well as

the use of risk assessment tools, as appropriate (see 5.2.6 and 5.2.7). The process simulation approach shall be included in the design/process review for the manufacturing of product.

b) Development of a process simulation strategy

1) A process simulation strategy shall be documented for a process that cannot be validated using a conventional process simulation approach as per ISO 13408-1.

NOTE See Figure 1 for an example of the development of a process simulation study.

2) If the process simulation approach outlined in ISO 13408-1 is not practicable, a rationale shall be documented including evidence that consideration was given during product and process development to:

— use of sterile liquid media as a substitute for product during process simulation, or

— direct media contact at the end of the process, i.e. into the sterile barrier system prior to final closure.

3) The entire aseptic process definition shall be included in the process simulation strategy. If the aseptic process is divided into sub-processes for the purposes of process simulation, the process simulation for each sub-process in total shall include all steps in the aseptic process.

4) Risk assessment shall be part of the life cycle of the aseptic process and shall be used to determine the process simulation strategy throughout the product/process life cycle.

5) The simulation options shall be selected and the process simulation strategy for the entire process shall be documented.

c) Process simulation throughout the product lifecycle

1) The initial process simulation approach shall be established during the development of the aseptic process and the first process simulation shall be performed in advance of the production of the first-in-human clinical products to verify acceptable aseptic processing conditions.

2) As the aseptic process is scaled-up and enhanced for later stages of clinical production, the process simulation approach shall be modified to address the changing aseptic process.

NOTE The aseptic process used for early clinical production is often manual and/or not optimized or scaled up for commercial production.

3) For commercial production, a process simulation study shall be designed and performed as part of the process validation.

4) Any change to the aseptic process which could add risk shall generate additional risk assessment and mitigation and a re-evaluation of the process simulation strategy. This shall include a re-evaluation of the process risk assessment.

d) Selection of sample(s) for testing for microbial contamination

1) Product:

Whenever possible, product shall be tested for microbial contamination. Product testing can take several forms. See Annex B for information.

If the product as designed cannot be tested, then prior to considering use of a surrogate product, the possibility of redesigning the product or process such that the actual product can be tested shall be assessed.

2) Surrogate product:

A surrogate product shall only represent the actual product if it constitutes an equivalent or greater challenge to the maintenance of asepsis than that provided by the actual product. The reason why the

actual product is unsuitable for testing shall be documented and the rationale for the selection of the surrogate product test sample described.

Surrogate product may be used for microbiological testing where product attributes preclude the use of actual product for testing. Examples of product attributes may include those that:

— are too large or irregularly shaped (e.g. osmotic pump);

— have antimicrobial properties (e.g. antibiotic stent);

— are rare and scarce (e.g. autologous chondrocyte);

— cause physical interference with the test method (e.g. product that breaks down in the growth medium generating particles that may be confused with microbial growth).

Selection and design of surrogate product shall reflect as much as possible the design of the actual product. Processing of surrogate product shall include all aseptic processing steps and interventions applied during manufacture of the actual product. See Annex B for guidance.

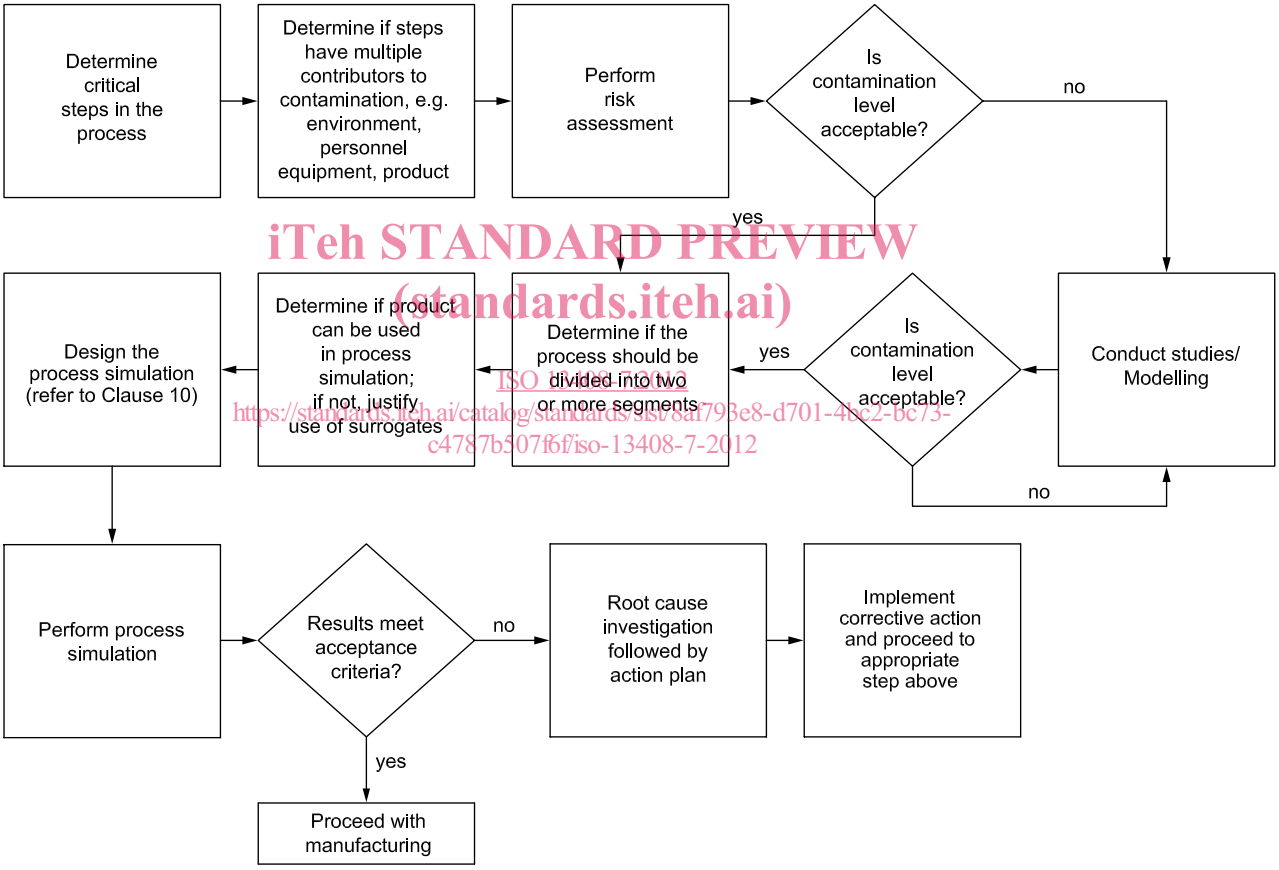

Figure 1 — Flow diagram of risk assessment process

e) Test methods for process simulation

The risk of contamination due to human intervention exists with all tests for microbial contamination. The selection of the test method shall consider both the sensitivity of the test as well as the number of interventions or manipulations. The risk assessment performed in the course of the process simulation study design (5.2.6.3) shall address the risks of introducing contamination during testing and define steps for reducing the likelihood of extrinsic contamination.

The test method shall be designed or selected based on product to be tested (actual or surrogate product). Test method development shall include consideration of suitable test options (see Annex C). The test method shall be validated.