

---

---

**Aseptic processing of health care  
products —**

**Part 1:  
General requirements**

*Traitement aseptique des produits de santé —*

*Partie 1: Exigences générales*



**PDF disclaimer**

This PDF file may contain embedded typefaces. In accordance with Adobe's licensing policy, this file may be printed or viewed but shall not be edited unless the typefaces which are embedded are licensed to and installed on the computer performing the editing. In downloading this file, parties accept therein the responsibility of not infringing Adobe's licensing policy. The ISO Central Secretariat accepts no liability in this area.

Adobe is a trademark of Adobe Systems Incorporated.

Details of the software products used to create this PDF file can be found in the General Info relative to the file; the PDF-creation parameters were optimized for printing. Every care has been taken to ensure that the file is suitable for use by ISO member bodies. In the unlikely event that a problem relating to it is found, please inform the Central Secretariat at the address given below.

This document is a preview generated by EVS



**COPYRIGHT PROTECTED DOCUMENT**

© ISO 2008

All rights reserved. Unless otherwise specified, no part of this publication may be reproduced or utilized in any form or by any means, electronic or mechanical, including photocopying and microfilm, without permission in writing from either ISO at the address below or ISO's member body in the country of the requester.

ISO copyright office  
Case postale 56 • CH-1211 Geneva 20  
Tel. + 41 22 749 01 11  
Fax + 41 22 749 09 47  
E-mail [copyright@iso.org](mailto:copyright@iso.org)  
Web [www.iso.org](http://www.iso.org)

Published in Switzerland

# Contents

Page

Foreword.....	v
Introduction .....	vi
1 Scope .....	1
2 Normative references .....	1
3 Terms and definitions.....	2
4 Quality system elements.....	7
4.1 General.....	7
4.2 Assignment of responsibilities .....	7
4.3 Calibration .....	7
5 Aseptic process definition .....	8
5.1 General.....	8
5.2 Risk management .....	8
6 Manufacturing environment.....	10
6.1 General.....	10
6.2 Manufacturing environment design .....	11
6.3 Layout .....	12
6.4 Material and personnel flow .....	14
6.5 HVAC system .....	15
6.6 Cleanroom qualification .....	17
6.7 Utility services and ancillary equipment .....	17
6.8 Environmental and personnel monitoring programmes .....	17
7 Equipment .....	21
7.1 Qualification .....	21
7.2 Maintenance of equipment .....	23
8 Personnel.....	23
8.1 General.....	23
8.2 Training for APA qualification .....	24
8.3 Gowning procedures .....	25
8.4 General employee health .....	26
9 Manufacture of the product .....	27
9.1 Attainment and maintenance of sterility .....	27
9.2 Duration of the manufacturing process .....	27
9.3 Aseptic manufacturing procedures .....	28
9.4 Cleaning and disinfection of facilities .....	28
9.5 Cleaning, disinfection and sterilization of equipment .....	30
10 Process simulation .....	31
10.1 General.....	31
10.2 Media selection and growth support .....	32
10.3 Simulation procedures .....	32
10.4 Incubation and inspection of media filled units .....	33
10.5 Initial performance qualification .....	33
10.6 Periodic performance requalification .....	34
10.7 Repeat of initial performance qualification .....	35
10.8 Documentation of process simulations .....	35
10.9 Disposition of filled product .....	36
11 Test for sterility .....	37

<b>11.1</b>	<b>General</b> .....	<b>37</b>
<b>11.2</b>	<b>Investigation of positive units from tests for sterility</b> .....	<b>37</b>
<b>Annex A</b> (informative)	<b>Example of a flow chart</b> .....	<b>38</b>
<b>Annex B</b> (informative)	<b>Typical elements of an aseptic process definition</b> .....	<b>39</b>
<b>Annex C</b> (informative)	<b>Examples of specific risks</b> .....	<b>40</b>
<b>Annex D</b> (informative)	<b>Comparison of classification of cleanrooms</b> .....	<b>41</b>
<b>Annex E</b> (informative)	<b>Specification for water used in the process</b> .....	<b>42</b>
<b>Annex F</b> (informative)	<b>Aseptic processing area</b> .....	<b>44</b>
<b>Bibliography</b> .....		<b>45</b>

This document is a preview generated by EVS

## 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 13408-1 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

This second edition cancels and replaces the first edition (ISO 13408-1:1998), which has been technically revised. Any normative and informative clauses on subjects which have meanwhile been addressed in Part 2 to Part 6 of ISO 13408 have been removed from this part.

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*

## Introduction

Health care products that are labelled “sterile” are prepared using appropriate and validated methods under stringent control as part of a quality management system. For pharmaceuticals and medical devices there might be various requirements including compliance with ISO standards, GMP regulations and pharmacopoeial requirements.

Wherever possible, health care products intended to be sterile should be sterilized in their final sealed container (terminal sterilization). ISO/TC 198 has prepared standards for terminal sterilization of health care products by irradiation (series ISO 11137), by moist heat (ISO 17665-1), by dry heat (ISO 20857, in preparation) and by ethylene oxide (ISO 11135-1).

When a health care product is intended to be sterile and cannot be terminally sterilized, aseptic processing provides an alternative. Presterilization of product, product parts and/or components and all equipment coming into direct contact with the aseptically-processed product is required. Aseptic processing intends to maintain the sterility of the pre-sterilized components and products during assembling. The resulting product is required to be sterile in its final container. Aseptic processing can also be used to prevent contamination of biological product or biological systems (e.g. tissues, vaccines).

While terminal sterilization involves the control of a well-defined process of known lethality delivered to the product and a sterility assurance level (SAL) can be extrapolated from sterilization data, this is not applicable to aseptic processing.

Examples of applications in which aseptic processing are used include:

- aseptic handling and filling of solutions, suspensions, semisolids and powders;
- aseptic handling, transfer and packaging of solid products including solid medical devices;
- aseptic handling, transfer and packaging of combination products;
- aseptic handling of tissues or biological production systems.

Sterilization procedures which render components and/or parts sterile as a prerequisite for further aseptic processing can be treated as separate procedures. They have to be evaluated and validated separately and it is important that their risk of failure is minimal. The aseptic process definition encompasses all production steps following the sterilization of product and components until the final container or package is sealed. To keep the aseptic process definition clear and workable, this part of ISO 13408 is focused on the risks to the maintenance of sterility.

It is important to control all possible sources of contamination in order to maintain the sterility of each and every component. To achieve this, a risk-based aseptic process definition is established encompassing each product and applied in a comprehensive way considering product, package design, environment and manufacturing process designs. The product is processed in a controlled environment where microbial and particulate levels are maintained at defined minimal levels and where human intervention is minimized. Validated systems, adequately trained personnel, controlled environments and well-documented systematic processes are applied to assure a sterile finished product.

The aseptic process is divided into unit operations (e.g. sterilization of product or components including sterile filtration, assembly of components, handling and storage of sterilized product) and it is necessary that potential sources of contamination from materials, components, product, personnel, facility, equipment and utilities such as water systems be considered and minimized. Only if all risks of contamination have been recognised, wherever possible minimized, eliminated or controlled and finally have been evaluated as

acceptable, can the controls on the aseptic process be considered to be acceptable. Appropriate validation of the specified elements of the aseptic process is needed, of which process simulation studies are an essential.

This revision of ISO 13408-1:1998 is intended to adopt this International Standard to the actual state of technology in the field.

This document is a preview generated by EVS

This document is a preview generated by EVS



# Aseptic processing of health care products —

## Part 1: General requirements

### 1 Scope

**1.1** This part of ISO 13408 specifies the general requirements for, and offers guidance on, processes, programmes and procedures for development, validation and routine control of the manufacturing process for aseptically-processed health care products.

**1.2** This part of ISO 13408 includes requirements and guidance relative to the overall topic of aseptic processing. Specific requirements and guidance on various specialized processes and methods related to filtration, lyophilization, clean-in place (CIP) technologies, sterilization in place (SIP) and isolator systems are given in other parts of ISO 13408.

**NOTE** This part of ISO 13408 does not supersede or replace national regulatory requirements, such as Good Manufacturing Practices (GMPs) and/or pharmacopoeial requirements that pertain in particular national or regional jurisdictions.

### 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 9001, *Quality management systems — Requirements*

ISO 11135-1, *Sterilization of health care products — Ethylene oxide — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO 11137-1, *Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO 11137-2, *Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose*

ISO 13408-2, *Aseptic processing of health care products — Part 2: Filtration*

ISO 13408-3, *Aseptic processing of health care products — Part 3: Lyophilization*

ISO 13408-4, *Aseptic processing of health care products — Part 4: Clean-in-place technologies*

ISO 13408-5, *Aseptic processing of health care products — Part 5: Sterilization in place*

ISO 13408-6, *Aseptic processing of health care products — Part 6: Isolator systems*

ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

ISO 14160, *Sterilization of single-use medical devices incorporating materials of animal origin — Validation and routine control of sterilization by liquid chemical sterilants*

ISO 14644-1:1999, *Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness*

ISO 14644-2, *Cleanrooms and associated controlled environments — Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1*

ISO 14644-3, *Cleanrooms and associated controlled environments — Part 3: Test methods*

ISO 14644-4, *Cleanrooms and associated controlled environments — Part 4: Design, construction and start-up*

ISO 14644-5, *Cleanrooms and associated controlled environments — Part 5: Operations*

ISO 14644-7, *Cleanrooms and associated controlled environments — Part 7: Separative devices (clean air hoods, gloveboxes, isolators and mini-environments)*

ISO 14698-1, *Cleanrooms and associated controlled environments — Biocontamination control — Part 1: General principles and methods*

ISO 14698-2, *Cleanrooms and associated controlled environments — Biocontamination control — Part 2: Evaluation and interpretation of biocontamination data*

ISO 14937, *Sterilization of health care products — General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices*

ISO 14971, *Medical devices — Application of risk management to medical devices*

ISO 17665-1, *Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices*

ISO 20857<sup>1)</sup>, *Sterilization of health care products — Dry heat — Requirements for the development, validation and routine control of a sterilization process for medical devices*

ICH Guidance for Industry — Q9 Quality Risk Management<sup>2)</sup>

### 3 Terms and definitions

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

#### 3.1 action level

established microbial or particulate monitoring results requiring immediate follow-up and corrective action

#### 3.2 airlock

room with interlocked doors designed to maintain pressure control between adjacent rooms of different cleanliness class

#### 3.3 alert level

established microbial or particulate monitoring results giving early warning of potential drift from normal operating conditions which are not necessarily grounds for definitive corrective action but which could require follow-up investigation

---

1) To be published.

2) Available at: <http://www.ich.org>