BS EN ISO 13408-1:2015

BSI Standards Publication

Aseptic processing of health care products

Part 1: General requirements

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National foreword

This British Standard is the UK implementation of EN ISO 13408-1:2015. It is identical to ISO 13408-1:2008, incorporating amendment 1:2013. It supersedes BS EN ISO 13408-1:2011+A1:2013 which is withdrawn.

The start and finish of text introduced or altered by amendment is indicated in the text by tags. Tags indicating changes to ISO text carry the number of the ISO amendment. For example, text altered by ISO amendment 1 is indicated by [A1] 〈A1〉.

The UK participation in its preparation was entrusted to Technical Committee CH/198, Sterilization and Associated Equipment and Processes.

A list of organizations represented on this committee can be obtained on request to its secretary.

This publication does not purport to include all the necessary provisions of a contract. Users are responsible for its correct application.

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Published by BSI Standards Limited 2015

ISBN 978 0 580 90760 9

ICS 11.080.01

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This British Standard was published under the authority of the Standards Policy and Strategy Committee on 31 August 2015.

Amendments issued since publication

Date	Text affected

EUROPEAN STANDARD

NORME EUROPÉENNE

EUROPÄISCHE NORM

EN ISO 13408-1

June 2015

ICS 11.080.01

English Version

Aseptic processing of health care products - Part 1: General requirements (ISO 13408-1:2008, including Amd 1:2013)

Traitement aseptique des produits de santé - Partie 1: Exigences générales (ISO 13408-1:2008, y compris Amd 1:2013)

Aseptische Herstellung von Produkten für die Gesundheitsfürsorge - Teil 1: Allgemeine Anforderungen (ISO 13408-1:2008, einschließlich Amd 1:2013)

This European Standard was approved by CEN on 20 May 2015.

CEN members are bound to comply with the CEN/CENELEC Internal Regulations which stipulate the conditions for giving this European Standard the status of a national standard without any alteration. Up-to-date lists and bibliographical references concerning such national standards may be obtained on application to the CEN-CENELEC Management Centre or to any CEN member.

This European Standard exists in three official versions (English, French, German). A version in any other language made by translation under the responsibility of a CEN member into its own language and notified to the CEN-CENELEC Management Centre has the same status as the official versions.

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CEN-CENELEC Management Centre: Avenue Marnix 17, B-1000 Brussels

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Ref. No. EN ISO 13408-1:2015 E

Foreword

The text of ISO 13408-1:2008, including Amd 1:2013 has been prepared by Technical Committee ISO/TC 198 “Sterilization of health care products” of the International Organization for Standardization (ISO) and has been taken over as EN ISO 13408-1:2015 by Technical Committee CEN/TC 204 “Sterilization of medical devices” the secretariat of which is held by BSI.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by December 2015, and conflicting national standards shall be withdrawn at the latest by December 2015.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. CEN [and/or CENELEC] shall not be held responsible for identifying any or all such patent rights.

This document supersedes EN ISO 13408-1:2011.

This document has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directives.

For relationship with EU Directives, see informative Annexes ZA, ZB and ZC, which are integral parts of this document.

The following referenced documents are indispensable for the application of this document. For undated references, the edition of the referenced document (including any amendments) listed below applies. For dated references, only the edition cited applies. However, for any use of this standard within the meaning of Annex ZA, ZB or ZC, the user should always check that any referenced document has not been superseded and that its relevant contents can still be considered the generally acknowledged state-of-art.

When an IEC or ISO standard is referred to in the ISO standard text, this should be understood as a normative reference to the corresponding EN standard, if available, and otherwise to the dated version of the ISO or IEC standard as listed below.

NOTE The way in which these referenced documents are cited in normative requirements determines the extent (in whole or in part) to which they apply.

Table — Correlation between normative references and dated EN and ISO standards

Normative references as listed in Clause 2 of the ISO standard	Equivalent dated standard	
	EN	ISO
ISO 9001	EN ISO 9001:2008	ISO 9001:2008
ISO 11135	EN ISO 11135:2014	ISO 11135:2014
ISO 11137-1	EN ISO 11137-1:2006 + A1:2013	ISO 11137-1:2006 + A1:2013
ISO 11137-2	EN ISO 11137-2:2013	ISO 11137-2:2013
ISO 13408-2	EN ISO 13408-2:2011	ISO 13408-2:2011
ISO 13408-3	EN ISO 13408-3:2011	ISO 13408-3:2011
ISO 13408-4	EN ISO 13408-4:2011	ISO 13408-4:2011
ISO 13408-5	EN ISO 13408-5:2011	ISO 13408-5:2011
ISO 13408-6	EN ISO 13408-6:2011 + A1:2013	ISO 13408-6:2011 + A1:2013

Normative references as listed in Clause 2 of the ISO standard	Equivalent dated standard	
	EN	ISO
ISO 13485	EN ISO 13485:2012	ISO 13485:2003
ISO 14160	EN ISO 14160:2011	ISO 14160:2011
ISO 14644-1	EN ISO 14644-1:1999	ISO 14644-1:1999
ISO 14644-2	EN ISO 14644-2:2000	ISO 14644-2:2000
ISO 14644-3	EN ISO 14644-3:2005	ISO 14644-3:2005
ISO 14644-4	EN ISO 14644-4:2001	ISO 14644-4:2001
ISO 14644-5	EN ISO 14644-5:2004	ISO 14644-5:2004
ISO 14644-7	EN ISO 14644-7:2004	ISO 14644-7:2004
ISO 14698-1	EN ISO 14698-1:2003	ISO 14698-1:2003
ISO 14698-2	EN ISO 14698-2:2003 + A1:2006	ISO 14698-2:2003 + A1:2006
ISO 14937	EN ISO 14937:2009	ISO 14937:2009
ISO 14971	EN ISO 14971:2012	ISO 14971:2007
ISO 17665-1	EN ISO 17665-1:2006	ISO 17665-1:2006
ISO 20857	EN ISO 20857:2013	ISO 20857:2013

Regarding the reference to ICH Q9: Guidance for Industry — Quality Risk Management, this should be considered to be the edition published in 2006.

According to the CEN-CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Former Yugoslav Republic of Macedonia, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and the United Kingdom.

Endorsement notice

The text of ISO 13408-1:2008, including Amd 1:2013 has been approved by CEN as EN ISO 13408-1:2015 without any modification.

Annex ZA
(informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 90/385/EEC on active implantable medical devices

This European Standard has been prepared under a mandate given to CEN/CENELEC by the European Commission and the European Free Trade Association to provide a means of conforming to Essential Requirements of the New Approach Directive 90/385/EEC on active implantable medical devices.

Once this standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the normative clauses of this standard given in Table ZA.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

NOTE 1 Where a reference from a clause of this standard to the risk management process is made, the risk management process needs to be in compliance with 90/385/EEC, as amended by 2007/47/EC. This means that risks have to be reduced 'as far as possible', 'to a minimum', 'to the lowest possible level', 'minimized' or 'removed', according to the wording of the corresponding essential requirement.

NOTE 2 The manufacturer's policy for determining **acceptable risk** must be in compliance with essential requirements 1, 4, 5, 8, 9 and 10 of the Directive.

NOTE 3 This Annex ZA is based on normative references according to the table of references in the European foreword, replacing the references in the core text.

NOTE 4 When an Essential Requirement does not appear in Table ZA.1, it means that it is not addressed by this European Standard.

Table ZA.1 — Correspondence between this European Standard and Directive 90/385/EEC

Clauses of this EN	Essential Requirements (ERs) of Directive 90/385/EEC	Qualifying remarks/Notes
4,5,6,7,8,9,10,11	7	Only attainment of sterility by aseptic processing is considered by this standard. This relevant Essential Requirement is only partly addressed in this European Standard. Design and packaging for maintenance of sterility during transportation and storage are not covered. Aspects of manufacture other than those related to sterilization are not covered.

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this Standard.

Annex ZB
(informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 93/42/EEC on medical devices

This European Standard has been prepared under a mandate given to CEN/CENELC by the European Commission and the European Free Trade Association to provide a means of conforming to Essential Requirements of the New Approach Directive 93/42/EEC on medical devices.

Once this standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the normative clauses of this standard given in Table ZB.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

NOTE 1 Where a reference from a clause of this standard to the risk management process is made, the risk management process needs to be in compliance with 93/42/EEC, as amended by 2007/47/EC. This means that risks have to be reduced 'as far as possible', 'to a minimum', 'to the lowest possible level', 'minimized' or 'removed', according to the wording of the corresponding essential requirement.

NOTE 2 The manufacturer's policy for determining **acceptable risk** must be in compliance with essential requirements 1, 2, 5, 6, 7, 8, 9, 11 and 12 of the Directive.

NOTE 3 This Annex ZA is based on normative references according to the table of references in the European foreword, replacing the references in the core text.

NOTE 4 When an Essential Requirement does not appear in Table ZA.1, it means that it is not addressed by this European Standard.

Table ZB.1 — Correspondence between this European Standard and Directive 93/42/EEC

Clauses of this EN	Essential Requirements (ERs) of Directive 93/42/EEC	Qualifying remarks/Notes
4,5,6,7,8,9,10,11	8.3	Only attainment of sterility by aseptic processing is considered by this standard. This relevant Essential Requirement is only partly addressed in this European Standard. Design and packaging for maintenance of sterility during transportation and storage are not covered. Aspects of manufacture other than those related to sterilization are not covered.
4,5,6,7,8,9,10,11	8.4	This relevant Essential Requirement is only partly addressed in this European Standard. Aspects of manufacture other than those related to sterilization are not covered.

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this Standard.

Annex ZC
(informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 98/79/EC on *in vitro* diagnostic medical devices

This European Standard has been prepared under a mandate given to CEN/CENELEC by the European Commission and the European Free Trade Association to provide a means of conforming to Essential Requirements of the New Approach Directive 98/79/EC on in vitro diagnostic medical devices.

Once this standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the normative clauses of this standard given in Table ZC.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

NOTE 1 Where a reference from a clause of this standard to the risk management process is made, the risk management process needs to be in compliance with 98/79/EC. This means that risks have to be reduced 'as far as possible', 'to a minimum', 'to the lowest possible level', 'minimized' or 'removed', according to the wording of the corresponding essential requirement.

NOTE 2 The manufacturer's policy for determining **acceptable risk** must be in compliance with essential requirements Part A: 1, 2 and 5; Part B: 1.2, 2, 3, 5, 6, and 7 of the Directive.

NOTE 3 This Annex ZA is based on normative references according to the table of references in the European foreword, replacing the references in the core text.

NOTE 4 When an Essential Requirement does not appear in Table ZA.1, it means that it is not addressed by this European Standard.

Table ZC.1 — Correspondence between this European Standard and Directive 98/79/EC

Clauses of this EN	Essential Requirements (ERs) of Directive 98/79/EC	Qualifying remarks/Notes
4,5,6,7,8,9,10,11	B.2.3	Only attainment of sterility by aseptic processing is considered by this standard. This relevant Essential Requirement is only partly addressed in this European Standard. Design and packaging for maintenance of sterility during transportation and storage are not covered. Aspects of manufacture other than those related to sterilization are not covered.

4,5,6,7,8,9,10,11	B.2.4	This relevant Essential requirement is addressed in this International Standard only with regard to: - sterilization, not covering other special microbiological state - devices for which aseptic processing is appropriate

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this Standard.

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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 13408-1 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*

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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, healthcare products intended to be sterile should be sterilized in their final sealed container (terminal sterilization). A1 ISO/TC 198 has prepared standards for terminal sterilization of health care products by irradiation (ISO 11137 series), by moist heat (ISO 17665 series), by dry heat (ISO 20857), by ethylene oxide (ISO 11135) and by liquid chemical sterilants (ISO 14160). A1

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

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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 ⟦A1⟩ component ⟨A1⟧.

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

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INTERNATIONAL STANDARD ISO 13408-1:2008+A1:2013(E)

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.

〚A1〛 *text deleted* 〚A1〛

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*

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