

Medical Device White Paper Series

# Sterilization – Regulatory requirements and supporting standards

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## Overview

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Sterile devices are free of viable microorganisms. Regulatory requirements for medical devices include particular requirements for devices supplied or intended to be used in a sterile state. These regulatory requirements relate both to general safety and performance requirements for the products and requirements for independent, third-party conformity assessment of the processes or instructions for achieving sterility. These regulatory requirements have been supported by a portfolio of standards on:

- designating products as sterile;
- validating and routinely controlling the sterilization process; and
- maintaining sterility over time with appropriate sterile barrier systems.

This paper provides an overview of these regulatory requirements and the standards that support them.



## Introduction

The European Medical Devices Regulation 2017/745 (MDR) includes general safety and performance requirements (GSPRs) in Annex I related to infection and microbial contamination. These GSPRs include requirements related to sterility. The In Vitro Diagnostic Medical Devices Regulation 2017/746 (IVDR) includes parallel requirements to the MDR. This paper focuses on the requirements of the MDR, but the IVDR requirements can be considered by analogy with the guidance contained here.

The regulations have specific roles for harmonized standards in demonstrating conformity. Article 8 in each regulation indicates that harmonized standards are those referenced in the Official Journal of the European Union. Devices in conformity with relevant harmonized standards are presumed to be in conformity with the requirements of the regulation covered by those standards. Additionally, the presumption of conformity also applies to system or process requirements, including those requirements relating to risk management.

In order for a standard to be harmonized under the regulations, a standardization request has to be agreed between the European Commission and the European Standards organizations – CEN and CENELEC. A draft of this standardization request was published by the European Commission. The European standards for designating medical devices as sterile, validating and routinely controlling particular sterilization processes and aseptic processing are on the list of standards to be harmonized in this draft standardization request. The deadline for adoption of most of the listed standards is 27 May 2024. This deadline applies to the standards for designating devices as sterile, validation and routine control of sterilization processes and aseptic processing.

Harmonized European standards include European Annex Zs that show the relationship between the requirements of the standard and the regulatory requirements in the European Directives or Regulations that are applicable to the scope of that standard. Work is in progress to include Annex Zs into new editions or amendments to the applicable sterilization and aseptic processing standards.

In addition, there are numerous references in the MDR to the manufacturer taking into account the generally acknowledged state of the art. The intention of the standards for sterilization is that these are regularly reviewed and updated as necessary in order to reflect this state of the art.

BSI has published over 70 documents on sterilization and associated equipment and processes. Of these, 46 are adoptions of ISO standards, most of which are common European and International standards. The other British Standards documents are 17 adoptions of European standards that do not have international equivalents and nine standalone British Standards. The standalone British Standards have been in place for a long time and remain either because there is no European or International standard on the topic or because there is a cross-reference to the document from another current standard. Work has been started recently to update:

- BS 3970, focusing on a specification for sterilizers using moist heat for fluids in sealed containers;
- BS 2646, giving requirements and performance tests for laboratory sterilizers; and
- BS 6256, focusing on a method for determination of methylene blue particulate penetration of packaging for terminally-sterilized medical devices.

## Requirements of the EU Medical Devices Regulation

The scope of the MDR is wider than that of the Medical Devices Directive that it replaces. A change in the definition of a medical device now includes products specifically intended for the cleaning, disinfection or sterilization of devices. These were previously covered as accessories.

Table 1 presents the GSPRs related to infection and microbial contamination and compares these with the essential requirements of the Medical Device Directive (93/42/EEC).

**Table 1** – Comparison of the requirements in relation to Infection and microbial contamination in the Medical Devices Regulation and the Medical Devices Directive

Medical Devices Regulation EU 2017/745 <sup>1</sup> Annex I General safety and performance requirements (GSPRs)	Medical Devices Directive 93/42/EEC <sup>2</sup> Annex I Essential Requirements (ERs)	Comments
<p>11.1. Devices and their manufacturing processes shall be designed in such a way as to eliminate or to reduce as far as possible the risk of infection to patients, users and, where applicable, other persons. The design shall:</p> <p>(a) reduce as far as possible and appropriate the risks from unintended cuts and pricks, such as needle stick injuries;</p> <p>(b) allow easy and safe handling;</p> <p>(c) reduce as far as possible any microbial leakage from the device and/or microbial exposure during use; and</p> <p>(d) prevent microbial contamination of the device or its content such as specimens or fluids.</p>	<p>8.1. The devices and manufacturing processes must be designed in such a way as to eliminate or reduce as far as possible the risk of infection to the patient, user and third parties. The design must allow easy handling and, where necessary, minimize contamination of the device by the patient or vice versa during use.</p>	<p>Addition of specific reference to needle-stick injuries. Added detail on 'minimizing contamination of the patient by the device and vice versa'.</p>
<p>11.2. Where necessary, devices shall be designed to facilitate their safe cleaning, disinfection, and/or re-sterilisation.</p>		<p>New emphasis on cleaning, disinfection and sterilization of reusable devices.</p>

<sup>1</sup> [Regulation \(EU\) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation \(EC\) No 178/2002 and Regulation \(EC\) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC](#)

<sup>2</sup> [COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices](#)



	<p><b>8.2.</b> Tissues of animal origin must originate from animals that have been subjected to veterinary controls and surveillance adapted to the intended use of the tissues. Notified bodies shall retain information on the geographical origin of the animals.</p> <p>Processing, preservation, testing and handling of tissues, cells and substances of animal origin must be carried out so as to provide optimal security. In particular, safety with regard to viruses and other transmissible agents must be addressed by implementation of validated methods of elimination or viral inactivation in the course of the manufacturing process.</p>	<p>MDD requirement related to transmissible spongiform encephalopathies (TSEs) now covered in GSPR 13 - Devices incorporating materials of biological origin and Directive 2003/32/EC<sup>3</sup>.</p>
<p><b>11.3.</b> Devices labelled as having a specific microbial state shall be designed, manufactured and packaged to ensure that they remain in that state when placed on the market and remain so under the transport and storage conditions specified by the manufacturer.</p>		<p>New requirement. As 11.4 below relates to sterile devices, this requirement appears to relate to specific microbial states other than sterility, such as devices that are supplied with a specified level of cleanliness, as disinfected, or with an absence of particular types of microorganisms.</p>
<p><b>11.4.</b> Devices delivered in a sterile state shall be designed, manufactured and packaged in accordance with appropriate procedures, to ensure that they are sterile when placed on the market and that, unless the packaging which is intended to maintain their sterile condition is damaged, they remain sterile, under the transport and storage conditions specified by the manufacturer, until that packaging is opened at the point of use. It shall be ensured that the integrity of that packaging is clearly evident to the final user.</p>	<p><b>8.3.</b> Devices delivered in a sterile state must be designed, manufactured and packed in a non-reusable pack and/or according to appropriate procedures to ensure that they are sterile when placed on the market and remain sterile, under the storage and transport conditions laid down, until the protective packaging is damaged or opened.</p>	<p>Added emphasis on the sterile barrier system.</p>

<sup>3</sup> [COMMISSION DIRECTIVE 2003/32/EC of 23 April 2003 introducing detailed specifications as regards the requirements laid down in Council Directive 93/ 42/EEC with respect to medical devices manufactured utilising tissues of animal origin](#)

<b>11.5.</b> Devices labelled as sterile shall be processed, manufactured, packaged and, sterilized by means of appropriate, validated methods.	<b>8.4.</b> Devices delivered in a sterile state must have been manufactured and sterilized by an appropriate, validated method.	Added emphasis on the sterile barrier system.
<b>11.6.</b> Devices intended to be sterilized shall be manufactured and packaged in appropriate and controlled conditions and facilities.	<b>8.5.</b> Devices intended to be sterilized must be manufactured in appropriately controlled (e. g. environmental) conditions.	Added emphasis on the packaging process for the sterile barrier system.
<b>11.7.</b> Packaging systems for non-sterile devices shall maintain the integrity and cleanliness of the product and, where the devices are to be sterilized prior to use, minimize the risk of microbial contamination; the packaging system shall be suitable taking account of the method of sterilization indicated by the manufacturer.	<b>8.6.</b> Packaging systems for non-sterile devices must keep the product without deterioration at the level of cleanliness stipulated and, if the devices are to be sterilized prior to use, minimize the risk of microbial contamination; the packaging system must be suitable taking account of the method of sterilization indicated by the manufacturer.	Essentially no changes.
<b>11.8.</b> The labelling of the device shall distinguish between identical or similar devices placed on the market in both a sterile and a non-sterile condition additional to the symbol used to indicate that devices are sterile.	<b>8.7.</b> The packaging and/or label of the device must distinguish between identical or similar products sold in both sterile and non-sterile condition.	Additional detail that the differentiation between sterile and non-sterile versions of similar devices is in the labelling and is more that the presence or absence of the sterile symbol.

The GSPRs of the MDR related to infection and microbial contamination show:

- increased detail in the wording;
- additional focus on reprocessing of devices;
- a new category of devices having a 'special microbial state'; and
- increased focus on the sterile barrier and its identification.

The requirements for conformity assessment require the intervention of a notified body for sterile medical devices of all classes. In addition, the MDR adds a conformity assessment requirement for a notified body to review the instructions for reprocessing of class I reusable surgical instruments.

## Designating of medical devices as sterile

The MDR presents requirements for sterile devices but does not provide a definition of the term 'sterile'. Sterile devices are free of viable microorganisms. The EN 556 series of standards defines requirements for designating device as sterile. Parts 1 and 2 of EN 556 provide requirements for terminally sterilized devices and aseptically produced devices respectively.

The standards related to designating devices as sterile and their status is shown in Table 2.

**Table 2** Standards related to designating medical devices as sterile

Standard reference	Standard title	Date of publication	Comments
EN 556-1	Sterilization of medical devices - Requirements for medical devices to be designated 'STERILE' - Part 1: Requirements for terminally sterilized medical devices	2001/AC: 2006	Amendment underway to add Annexes ZD and ZE for the MDR and IVDR.
EN 556-2	Sterilization of medical devices. Requirements for medical devices to be designated «STERILE». Requirements for aseptically processed medical devices	2015	
ISO TS 19930	Guidance on aspects of a risk-based approach to assuring sterility of terminally-sterilized, single-use health care products	2017	Guidance document and not intended to provide any presumption of conformity with European regulatory requirements.

EN 556-1 is the European standard specifying requirements for designating a terminally-sterilized device as sterile. It has also been adopted in a number of countries outside Europe, for example Australia and China. EN 556-1 specifies that a probability of a viable microorganism on a device of  $10^{-6}$  or less (e.g.  $10^{-7}$ , et seq.) has to be achieved in order to designate a terminally sterilized medical device as sterile. The probability of survival of a single microorganism is also known as the sterility assurance level (SAL).

There can be, however, devices that are unable to withstand a terminal sterilization process achieving this probability. This might be because some or all of the materials that constitute the device are sensitive to traditional sterilization processes, for example cellular or biologically based components. EN 556-1 includes an explanatory note that indicates that permission for acceptance of a probability greater than  $10^{-6}$  (e.g.  $10^{-5}$ ) can be sought through appropriate regulatory bodies. Such permission requires consideration of the individual situation, including the risk assessment undertaken by the manufacturer of the device. However, EN 556-1 gives no guidance on criteria that might be considered in seeking such approval and there is no alignment on how such devices should be labelled.

ISO/TS 19930:2017 (see Table 2) provides:

- background information on assurance of sterility and sterility assurance level,
- guidance on strategies that can allow the achievement of a maximal SAL of  $10^{-6}$ , and,
- general guidance on the considerations to be taken into account in selecting a SAL for a health care product that is unable to withstand terminal sterilization to meet the general requirement to achieve maximally a SAL of  $10^{-6}$ .

ISO/TS 19930 has not yet been adopted as a European Standard. It is a guidance document and not intended to provide any presumption of conformity with European regulatory requirements. This topic is contentious for some regulatory agencies, conformity assessment bodies, manufacturers and national standards bodies. This TS does not relax the regulatory and quality requirements to claim that a product is sterile. Its purpose is to bridge a gap in existing standards and regulations. ISO TS 19930 provides guidance on technical aspects when considering an alternative SAL to  $10^{-6}$  for identified high clinical need, terminally sterilized devices unable to withstand the processing conditions necessary to achieve maximally a SAL of  $10^{-6}$ .

When terminal sterilization is not possible, aseptic processing provides an alternative means of achieving a sterile device. Aseptic processing is based on preventing contamination of sterile items. Aseptic processing is not based on inactivation of microorganisms and so the concept of extrapolation of a probability of survival of a microorganism does not apply. EN 556-2 provides requirements for designating an aseptically-processed medical device as sterile. The EN ISO 13408 series of standards (see section on Aseptic Processing of medical devices and Table 4) provide means to support conformance with EN 556-2.





## Validation and routine control of sterilization processes

There is a portfolio of European Standards for development, validation and routine control of sterilization processes. These standards are European adoptions of International Standards. The standards and their status are listed in Table 3. These standards for validation and routine control of sterilization are listed in the draft Standardization Request of priority standards to be harmonized for the MDR.

**Table 3** Standards for development, validation and routine control of a sterilization process

Standard reference	Standard title	Date of publication	Comments
EN 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	2009	Provides structure used in all the standards for validation and routine control of sterilization processes. Gives requirements for any process which does not have a specific standard for validation and routine control.
EN ISO 11135	Sterilization of health-care products - Ethylene oxide - Requirements for the development, validation and routine control of a sterilization process for medical devices	2014 AMD1: 2019	2019 amendment changes the Annex on single batch validation and adds Annexes ZD and ZE for the MDR and IVDR.
ISO TS 21387	Sterilization of health care products – Ethylene oxide - Guidance on the requirements for processes using parametric release		Technical Specification due for publication in 2020
EN ISO 11137-1:	Sterilization of health care products - Requirements for the development, validation and routine control of a sterilization process for medical devices - Radiation - Part 1: Requirements	2006/AMD1 2013, AMD2 2019	2019 amendment addresses use of measurement uncertainty in product release and adds Annexes ZD and ZE for the MDR and IVDR.

EN ISO 11137-2	Sterilization of health care products - Requirements for the development, validation and routine control of a sterilization process for medical devices - Radiation - Part 2: Establishing the sterilization doses	2013	Provides the methods for establishing a sterilization dose for sterilization by irradiation.
BS EN ISO 11137-3	<b>Sterilization of health care products. Radiation. Guidance on dosimetric aspects of development, validation and routine control</b>	2017	Provides guidance on the application of dose measurements (dosimetry) during all stages of the sterilization process.
ISO CD TS 11137-4	Sterilization of health care products - Radiation - Part 4: Guidance on process control		Technical specification in development.
ISO TS 13004	Sterilization of health care products – Radiation – Substantiation of a selected sterilization dose: Method $VD_{max}^{SD}$	2013	Extends the method for substantiation of a sterilization dose for radiation sterilization from the use of 15kGy and 25kGy given in EN ISO 11137-2.
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	2006	Revision started to combine parts 1, 2 and 3.
CEN/ISO TS 17665-2	Sterilization of health care products - Moist heat - Part 2: Guidance on the application of ISO 17665-1	2009	
ISO TS 17665-3	Sterilization of health care products - Steam sterilization - Part 3: Product families	2013	
EN ISO 20857	Sterilization of health care products – Dry heat – Requirements for the development, validation and routine control of an industrial sterilization process for medical devices	2013	

<b>EN ISO 25424</b>	Sterilization of medical devices – Low temperature steam and formaldehyde – Requirements for development, validation and routine control of a sterilization process for medical devices	2019	Includes Annexes ZD and ZE for the MDR and IVDR.
<b>EN ISO 14160</b>	Sterilization of health care products - Liquid chemical sterilizing agents for single-use medical devices utilizing animal tissues and their derivatives - Requirements for characterization, development, validation and routine control of a sterilization process for medical devices	2011	New edition of the standard awaiting publication. New edition includes Annexes ZD and ZE for the MDR and IVDR.
<b>ISO NP 22441</b>	Sterilization of health care products - Low temperature vaporized hydrogen peroxide - Requirements for the development, validation and routine control of a sterilization process for medical devices		Standard in development

The standards are intended to ensure that the sterilization process is reliable and reproducible. Reliability and reproducibility provide confidence that predictions can be made that there is an acceptable, low probability of there being a viable microorganism present on device after sterilization. These standards provide a means to demonstrate conformity with the requirements for sterility for terminally-sterilized medical devices specified in EN 556-1.

All the standards for validation and routine control have a common format and use a common set of definitions. The common structure includes:

- Sterilizing agent characterization – defines the sterilizing agent
- Process and equipment characterization – defines the entire sterilization process and the equipment necessary to deliver the sterilization process safely and reproducibly
- Product definition – defines the product to be sterilized, including the microbiological quality of the product prior to sterilization and the manner in which product is packaged and presented for sterilization
- Process definition – details a specification for the sterilization process to be applied to the defined product
- Validation – demonstrates that the sterilization process established in the process definition can be delivered effectively and reproducibly to the sterilization load. Validation consists of installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ)
- IQ is undertaken to demonstrate that the sterilization equipment and any ancillary items have been supplied and installed in accordance with their specification

- OQ is carried out either with unloaded equipment or using appropriate test materials to demonstrate the capability of the equipment to deliver the sterilization process that has been defined
- PQ is the stage of validation that uses product to demonstrate that the equipment consistently operates in accordance with predetermined criteria and the process yields product that is sterile and meets the specified requirements
- Routine monitoring and control – demonstrates that the validated and specified sterilization process has been delivered to the product
- Product release from sterilization – specifies the procedure for product release from sterilization
- Maintaining process effectiveness – addresses ensuring the consistent condition of product presented for sterilization, maintenance and calibration of equipment, assessment of changes to product, process or sterilizing equipment and periodic requalification

An amendment to EN ISO 11135 for ethylene oxide sterilization was published in late 2019. The amendment changes one of the Annexes in the standard – Annex E: Single batch release. This annex covers requirements for releasing product from a sterilization process that is not in routine production – for example, during design and development, including product for clinical investigation. This approach can be applicable if a new product cannot be assigned to an existing family of products for the purposes of sterilization validation. The changes to Annex E provide more detail, in particular on the need to select a suitable sample of products for:

- evaluating bioburden;
- determining a suitable process challenge device (PCD) with biological indicators (BIs) to be incorporated within the sterilization load;
- performing tests of sterility;
- determining ethylene oxide residuals;
- performing stability tests, functionality tests, testing for biological safety and any other necessary evaluations such as tests for the presence of bacterial endotoxins.

The approach described in Annex E is to expose the sterilization load, incorporating PCDs with BIs, and temperature and humidity sensors, to an ethylene oxide process with the exposure time set to half the sterilization cycle time (called a half cycle). The BIs from the PCDs are tested and product items from the half cycle undergo a test of sterility. After aeration and equilibration to ambient conditions, the load from the half cycle undergoes a full sterilization cycle with temperature and humidity sensors and new PCDs incorporating BIs included. Product is tested for functionality and ethylene oxide residuals after exposure to both the half cycle and full sterilization cycle. Criteria for release of product include, but are not limited to:

- conformance to the process specification for the half cycle and full sterilization cycle;
- no growth from BIs from the half cycle and full sterilization cycle;
- no positive tests of sterility from the half cycle; and
- ethylene oxide residual levels complying with EN ISO 10993-7, *Biological evaluation of medical devices - Ethylene oxide sterilization residuals* after exposure to both the half cycle and full sterilization cycle.





## Aseptic processing of medical devices

As indicated above, aseptic processing provides an alternative means of achieving a sterile device when terminal sterilization is not possible and the EN ISO 13408 series of standards provide means to support conformance with EN 556-2. The standards in the EN ISO 13408 series and their status are indicated in Table 4.

**Table 4** Standards for aseptic processing

Standard reference	Standard title	Date of publication	Comments
EN ISO 13408-1	Aseptic processing of health care products – Part 1: General requirements	2011/AMD1 2013	Revision just starting
EN ISO 13408-2	Aseptic processing of health care products – Part 2: Filtration	2018	
EN ISO 13408-3	Aseptic processing of health care products – Part 3: Lyophilization	2011	
EN ISO 13408-4	Aseptic processing of health care products – Part 4: Clean-in-place technologies	2011	
EN ISO 13408-5	Aseptic processing of health care products – Part 5: Sterilization-in-place	2011	
EN/ISO 13408-6	Aseptic processing of health care products – Part 6: Isolator systems	2011	Under revision
EN ISO 13408-7	Aseptic processing of health care products – Part 7: Aseptic qualification of solid medical devices and combination medical devices	2015	
ISO 18362	Manufacture of cell-based health care products – Control of microbial risks during processing	2016	

EN ISO 13408 presents general requirements of aseptic processing in Part 1. Subsequent parts of the series provide additional details on specific aspects of aseptic processing. Aseptic processing of solid medical devices can present particular issues and EN ISO 13408-7 is specifically focused on solid devices.

ISO 18362 addresses the processing of cell-based products. A cell-based health care product comprises cells or cell-derived biological entities as an essential ingredient. Cell-based or cell derived starting material can be viable or non-viable and of human, animal, microbial or plant origin. Such products are classified as medicines, medical devices, biologics or combination products depending on the international, national and/or regional regulations that govern their supply. Cell-based products can have limited ability to withstand sterilization and purification methods. ISO 18363 describes the minimum elements necessary for a risk-based approach to the processing to reduce the potential for an increase in intrinsic contamination of product and to avoid extrinsic contamination of product.



## Microbiological methods

There are several microbiological methods that are used in developing, validating and routinely controlling sterilization processes. These methods relate to estimation of the population of microorganisms on a product prior to sterilization, determining the bioburden and determining the presence or absence of viable microorganism through performing a test of sterility. The principles for conducting these microbiological methods are described in the EN ISO 11737 series of standards and are outlined in Table 5.

**Table 5** Standards for microbiological methods used in development, validation and routine control of sterilization

Standard reference	Standard title	Date of publication	Comments
EN ISO 11737-1	Sterilization of medical devices. Microbiological methods. Determination of the population of microorganisms on products	2018	Amendment in process

<b>EN ISO 11737-2</b>	Sterilization of medical devices. Microbiological methods. Tests of sterility performed in the validation of a sterilization process	2009	Revised edition awaiting publication
<b>ISO 11737-3</b>	Sterilization of medical devices – Microbiological methods – Part 3: Bacterial endotoxin testing		In preparation
<b>ISO TS 22456</b>	Sterilization of healthcare products – Microbiological Methods - Guidance on conducting bioburden determinations and tests of sterility for tissue-based products		In preparation

The third edition of EN ISO 11737-1 was published in 2018. It replaces the second edition from 2006 and incorporates the Technical Corrigendum issued in 2007. The changes from the previous edition include:

- introducing the term 'bioburden spikes' as a feature of bioburden data and providing examples;
- clarifying that package testing is not typically performed unless the package is an integral part of the product;
- providing more information on the most probable number (MPN) technique and its applications;
- giving details of ways to improve the limit of detection and correct use of the data;
- adding a table with criteria for selection of an approach to estimating the efficiency of bioburden recovery and explaining the use of the correction factor;
- providing more information on the application and performance of a suitability test for a bioburden method;
- introducing rules for direct plate counts, estimated counts and counts beyond the ideal range; and
- adding clarification on where typical responsibilities reside for the manufacturer or an external laboratory

A new edition of EN ISO 11737-2 on tests of sterility is at the final stages of balloting. This will become the third edition and will replace the 2009 edition. Some changes parallel those incorporated in EN ISO 11737-1. Others include adding requirements that:

- the interval between manufacturing the device and sterilizing it reflects routine processing timelines; and
- product remains immersed in the culture media

In addition, guidance has been added on:

- controlling the environment for performing tests of sterility;
- identifying the microorganism when microbial growth is detected in a test of sterility; and
- demonstrating ongoing method suitability periodically to ensure that an accumulation of minor changes has not occurred over time

New work has started to prepare EN ISO 11737-3 on bacterial endotoxin testing. This will specify general criteria for determination of bacterial endotoxins on or in raw materials, components or health care products. It applies to use of bacterial endotoxin test methods with amebocyte lysate reagents from *Limulus polyphemus* or *Tachypleus tridentatus*. It is not applicable to the evaluation of pyrogens other than bacterial endotoxin and does not include other endotoxin detection methodologies such as monocyte activation and recombinant Factor C.



## Sterile barrier systems

The MDR gives a greater focus on sterile barrier systems that maintain the sterility of a device to the point of use. The standards for packaging for sterile devices and their status are shown in Table 6.

**Table 6** Standards for sterile barrier systems

Standard reference	Standard title	Date of publication	Comments
EN ISO 11607-1	Packaging for terminally sterilized medical devices. Requirements for materials, sterile barrier systems and packaging systems	2020	Provides requirements and test methods for materials, preformed sterile barrier systems, sterile barrier systems and packaging systems that are intended to maintain sterility of terminally sterilized medical devices until the point of use. Amendment under consideration to incorporate European Annexes and relationship with the Medical Devices Regulation.
EN ISO 11607-2	Packaging for terminally sterilized medical devices. Validation requirements for forming, sealing and assembly processes	2020	Gives requirements for the development and validation of processes for packaging medical devices that are terminally sterilized. These processes include forming, sealing and assembly of preformed sterile barrier systems, sterile barrier systems and packaging systems. Amendment under consideration to incorporate European Annexes and relationship with the Medical Devices Regulation.

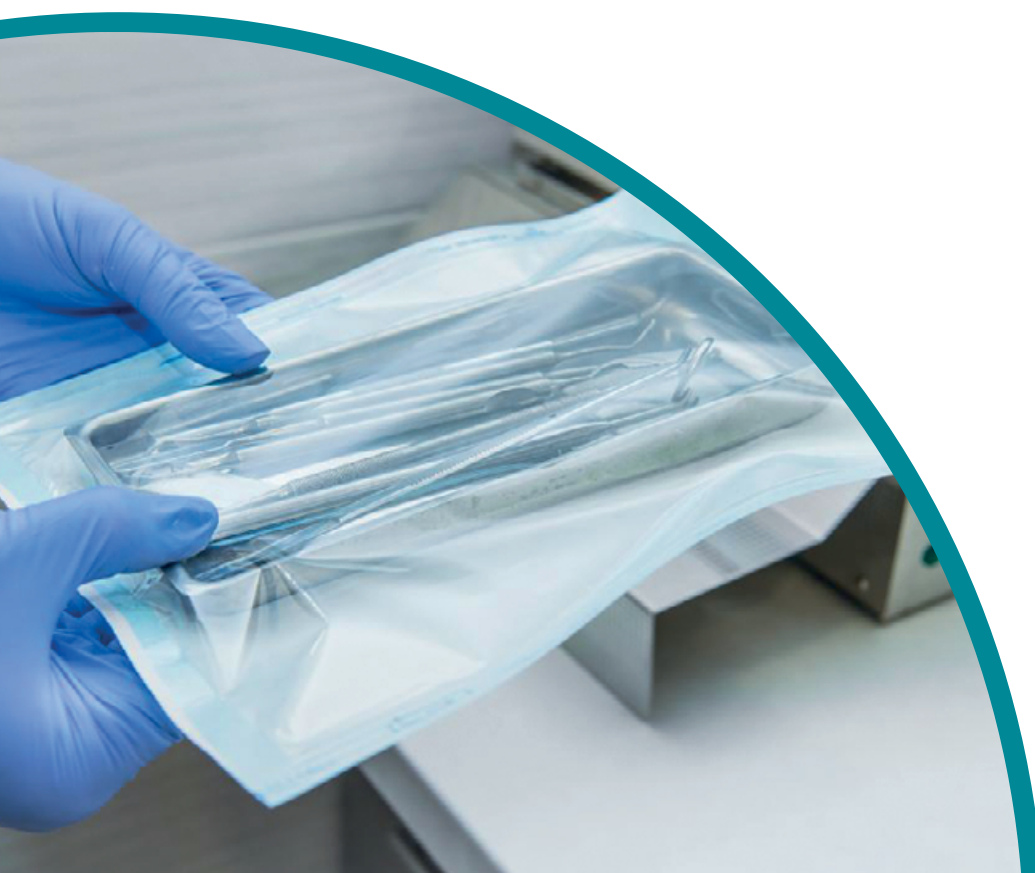


<b>EN 868-2</b>	Packaging materials for terminally sterilized medical devices. Part 2: Sterilization wrap - Requirements and test methods	2017	The EN 868 series of standards comprises Parts 2 to 10. The series provides requirements and test methods for a range of specific materials and configurations of sterile barrier systems and can be used to demonstrate compliance with one or more of the general requirements specified in EN ISO 11607-1.
<b>EN 868-3</b>	Packaging materials for terminally sterilized medical devices. Part 3: Paper for use in the manufacture of paper bags (specified in EN 868-4) and in the manufacture of pouches and reels (specified in EN 868-5) - Requirements and test methods	2017	
<b>EN 868-4</b>	Packaging materials for terminally sterilized medical devices. Part 4: Paper bags - Requirements and test methods	2017	
<b>EN 868-5</b>	Packaging materials for terminally sterilized medical devices. Part 5: Sealable pouches and reels of porous materials and plastic film construction - Requirements and test methods	2018	
<b>EN 868-6</b>	Packaging for terminally sterilized medical devices - Part 6: Paper for low temperature sterilization processes - Requirements and test methods	2017	
<b>EN 868-7</b>	Packaging for terminally sterilized medical devices - Part 7: Adhesive coated paper for low temperature sterilization processes - Requirements and test methods	2017	
<b>EN 868-8</b>	Packaging materials for terminally sterilized medical devices. Part 8: Re-usable sterilization containers for steam sterilizers conforming to EN 285 -Requirements and test methods	2018	
<b>EN 868-9</b>	Packaging materials for terminally sterilized medical devices. Part 9: Uncoated nonwoven materials of polyolefines for use in the manufacture of sealable pouches, reels and lids - Requirements and test methods	2018	
<b>EN 868-10</b>	Packaging materials for terminally sterilized medical devices. Part 10: Adhesive coated nonwoven materials of polyolefines for use in the manufacture of sealable pouches, reels and lids - Requirements and test methods	2018	

The EN ISO 11607 series of standards are listed in the draft standardization request for the MDR. EN ISO 11607 has two parts, in which:

- Part 1 specifies general requirements and test methods for materials, preformed sterile barrier systems, sterile barrier systems and packaging systems that are intended to maintain sterility of terminally sterilized medical devices to the point of use; and
- Part 2 specifies validation requirements for forming, sealing and assembly processes

The EN 868 standards also have the general title Packaging for terminally sterilized medical devices. EN 868-1:1997, which provided the general requirements for packaging materials for sterile medical devices, was withdrawn in 2006 and replaced by EN ISO 11607-1. The remaining parts in the EN 868 standards remain, and revised editions have been published in 2018. This series comprises Parts 2 to 10. The EN 868 series can be used to demonstrate compliance with one or more of the general requirements specified in EN ISO 11607-1. The EN 868 series of standards is intended to assist hospital users and manufacturers of medical devices to identify materials for sterile barrier systems and purchase materials and products to be used for medical devices to be sterilized.



## Indicators for sterilization

The specific procedures for validation and routine control of sterilization can require the use of standardized test pieces such as biological or chemical indicators for sterilization.

The standards for biological indicators are shown in Table 7 and for chemical indicators in Table 8.

**Table 7** Standards for biological indicators for sterilization

Standard reference	Standard title	Date of publication	Comments
EN ISO 11138-1	Sterilization of health care products - Biological indicators - Part 1: General requirements	2017	Part 1 if the ISO 11138 series specifies general requirements for production, labelling, test methods and performance characteristics of biological indicators and their components, to be used in the validation and routine monitoring of sterilization processes.
EN ISO 11138-2	Sterilization of health care products - Biological indicators - Part 2: Biological indicators for ethylene oxide sterilization processes	2017	Subsequent parts of the EN ISO 11138 series give specific requirements for biological indicators for particular sterilization processes.
EN ISO 11138-3	Sterilization of health care products - Biological indicators - Part 3: Biological indicators for moist heat sterilization processes	2017	
EN ISO 11138-4	Sterilization of health care products - Biological indicators - Part 6: Biological indicators for dry heat sterilization processes	2017	
EN ISO 11138-5	Sterilization of health care products - Biological indicators - Part 5: Biological indicators for low-temperature-steam-formaldehyde sterilization	2017	Amendment in preparation
ISO 11138-6	Sterilization of health care products - Biological Indicators - Part 6: Biological indicators for hydrogen peroxide sterilization processes		Standard in development

<b>EN ISO 11138-7</b>	Sterilization of health care products - Biological indicators - Part 7: Guidance for the selection, use and interpretation of results	2019	Provides guidance for the selection, use and interpretation of results from application of biological indicators when used in the development, validation and routine monitoring of sterilization processes.
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**Table 8** Standards for chemical indicators for sterilization

Standard reference	Standard title	Date of publication	Comments
<b>EN ISO 11140-1</b>	Sterilization of health care products - Chemical indicators - Part 1: General requirements	2014	EN ISO 11140-1 gives general requirements and test methods for indicators that show exposure to sterilization processes by means of physical and/or chemical change of substances, and which are used to monitor the attainment of one or more of the process parameter(s) specified for a sterilization process. They are not dependent for their action on the presence or absence of a living organism.
<b>ISO 11140-2</b>	Sterilization of health care products - Chemical indicators - Part 2: Test equipment and methods	Withdrawn	ISO 18472:2006 now specifies the requirements for test equipment to be used to test chemical and biological indicators for steam, ethylene oxide, dry heat and vaporized hydrogen peroxide processes for conformity to the requirements given in <ul style="list-style-type: none"> <li>• ISO 11140-1 for chemical indicators, or</li> <li>• ISO 11138 series for biological indicators</li> </ul>
<b>EN ISO 11140-3</b>	Sterilization of health care products - Chemical indicators - Part 3: Class 2 indicator systems for use in the Bowie and Dick-type steam penetration test	2007/ Cor.1: 2007	
<b>EN ISO 11140-4</b>	Sterilization of health care products - Chemical indicators - Part 4: Class 2 indicators as an alternative to the Bowie and Dick-type test for detection of steam penetration	2007	

<b>ISO 11140-5</b>	Sterilization of health care products - Chemical indicators - Part 5: Class 2 indicators for Bowie and Dick-type air removal tests.	2007	
<b>EN ISO 11140-6</b>	Sterilization of health care products – Chemical indicators – Part 6: Class 2 indicator systems and process challenge devices for use in performance testing for sterilizers		In preparation
<b>EN ISO 15882</b>	Chemical indicators - Guidance on the selection, use, and interpretation of results	2008	Provides guidance for the selection, use and interpretation of results of chemical indicators used in process definition, validation and routine monitoring and overall control of sterilization processes.

The change in the definition of a medical device in the MDR means that products for cleaning, disinfection or sterilization are now within the definition of a device. Accessories to such products, previously outside the scope of the Directive, are now covered by the MDR. Consequently, sterilization indicators that were previously outside the Directive can now be considered accessories to the sterilizing equipment (now considered a device) and are thus covered by the MDR. However, the exclusion in the scope of the Regulation for products that contain or consist of living microorganisms introduces a situation where biological indicators for sterilization could be considered excluded from the Regulation, but chemical indicators for sterilization considered as accessories.

## Conclusion

The MDR has specific requirements for medical devices designated as sterile, in relation to the validation and routine control of the sterilization process and notified body involvement in the conformity assessment process. The requirements for designating devices as sterile and validating and routinely controlling sterilization processes are supported by a series of European standards. These standards are generally European adoptions of International standards. Many of the sterilization standards are included in the draft standardization request from the European Commission for standards to be harmonized to support the MDR. The standards represent a common understanding of how to meet the regulatory requirements related to sterilization. Manufacturers of sterile devices should keep up to date with developments in the sterilization standards as these evolve to keep aligned with the state of the art.



## Author

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**Eamonn Hoxey** is a technical author, trainer and consultant on a range of life science areas including regulatory compliance, quality management, sterility assurance and standards development. Eamonn worked for Johnson & Johnson (J&J) for 17 years in positions of increasing responsibility for Quality and Regulatory Compliance for medical devices, pharmaceuticals and consumer products. These included Vice President of Compliance, Vice President of Market Quality and Vice President of Quality & Compliance Strategic Programs, leading quality implementation for the EU medical devices regulation for J&J's Medical Devices companies. Prior to joining J&J, Eamonn spent 16 years with the UK Medical Devices Agency, including six years as Head of Device Technology and Safety. Eamonn is chair of CEN TC 204, Sterilization of medical devices, and chaired ISO TC 198, Sterilization of health care products, from 2011 to 2019. Eamonn is also a past chair of ISO TC 210, 'Quality management and related general aspects for medical devices', and the current chair of the Board of Directors of The Association for the Advancement of Medical Instrumentation (AAMI). He received the BSI Wolfe-Barry medal in 2016 for his contribution to standards development.

## Peer reviewers

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**Peter Strain** worked for 25 years at Sterigenics, formerly Griffith Micro Science, retiring in December 2018. Prior to his retirement, Peter was Vice President EO Technical Services at Sterigenics, which involved working with Sterigenics' and customer validation experts to design and validate compliant sterilization processes for medical devices and other products.

Peter is an active member of the Association of British Healthcare Institute Sterilization and Microbiology Working Group. He has represented BSI for 15 years on ISO TC 198 WG1, currently as Convenor, which developed ISO 11135 and other documents relating to Ethylene Oxide sterilization.

**Paul Sim** has worked in the healthcare industry for over 35 years, joined BSI in 2010 to lead the organization in Saudi Arabia where it had been designated as a Conformity Assessment Body. Later, he managed BSI's Unannounced Audits programme. Since October 2015, he has been working with both the Notified Body and Standards organizations looking at how best to use the knowledge, competencies and expertise in both. Previously he held senior RA/QA leadership positions at Spacelabs Healthcare, Teleflex Medical, Smiths Medical and Ohmeda (formerly BOC Group healthcare business). Paul is a member of the Association of British Healthcare Industries (ABHI) Technical Policy Group and Convenor of the ABHI ISO TC 210 Mirror Group. He is Convenor of the BSI Committee that monitors all of the work undertaken by ISO TC 210, and Convenor of the BSI Subcommittee dealing with quality systems. As UK Delegation Leader to ISO TC 210, he is also actively involved in the work of national, European and international standards' committees.

## Published white papers





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- *Do You Know the Requirements and Your Responsibilities for Medical Device Vigilance Reporting? – A Detailed Review on the Requirements of MDSAP Participating Countries in Comparison With the European Medical Device Regulation 2017/745*, Cait Gatt and Suzanne Halliday
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## Forthcoming white papers

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-  *The Convergence of Pharma and Medical Devices*, Barbara Nasto (working title)
-  *Clinical Investigation* – Maria Donawa (working title)
-  *Phthalates and Endocrine Disruptors* – Benjamin Seery (working title)
-  *UDI – what is required now and how to manage it* – Lena Cordie (working title)

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BSI (British Standards Institution) is the business standards company that equips businesses with the necessary solutions to turn standards of best practice into habits of excellence. Formed in 1901, BSI was the world's first National Standards Body and a founding member of the International Organization for Standardization (ISO). Over a century later it continues to facilitate business improvement across the globe by helping its clients drive performance, manage risk and grow sustainably through the adoption of international management systems standards, many of which BSI originated. Renowned for its marks of excellence including the consumer recognized BSI Kitemark™, BSI's influence spans multiple sectors including aerospace, construction, energy, engineering, finance, healthcare, IT and retail. With over 70,000 clients in 150 countries, BSI is an organization whose standards inspire excellence across the globe.

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