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Overview of ISO 11135:2014 and Medical Device Sterilization

Key changes to sterilization processes and procedures for the US and Europe



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The ISO 11135 Standard and Medical Devices

Until July 2014, ISO 11135-1:2007 was the international standard used for the process management and validation requirements of Ethylene Oxide (EO) sterilization, a popular method for sterilizing medical devices. The new ISO 11135:2014 replaced the previous version and is gaining worldwide recognition.

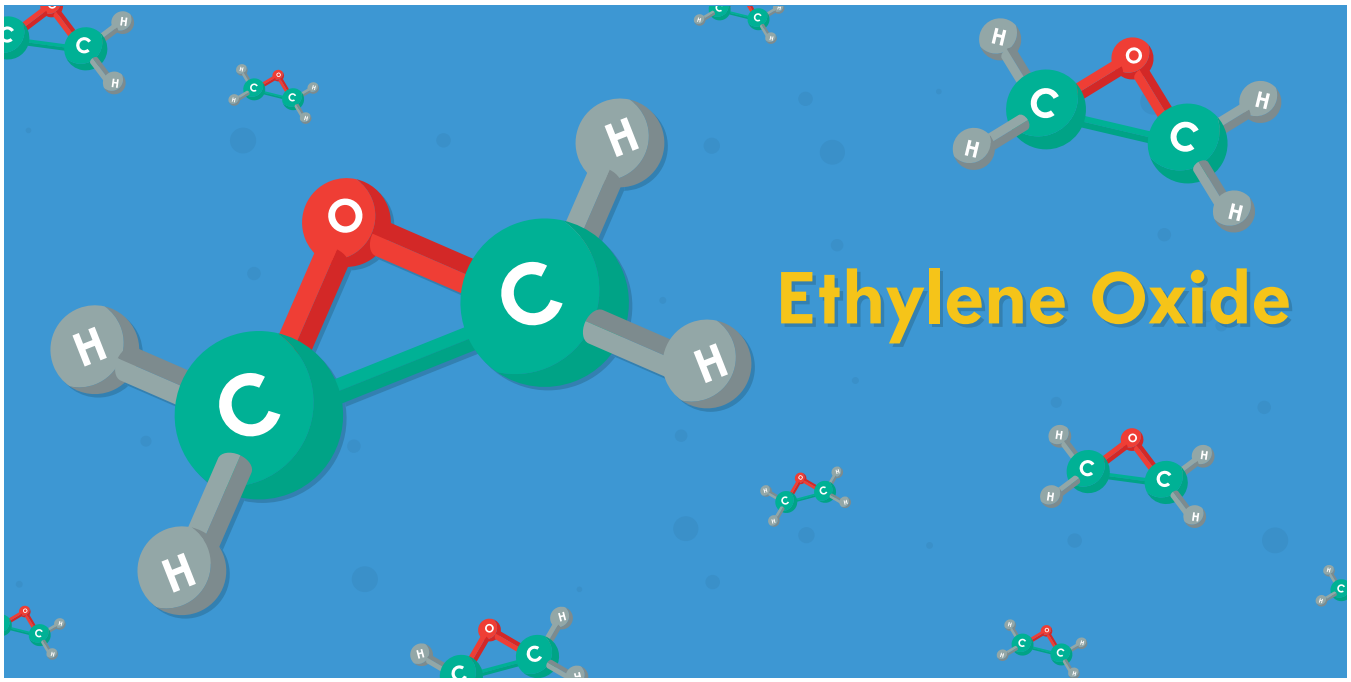
For instance, in the United States, ISO 11135:2014 is a recognized consensus standard under Recognition Number 14-452, according to the FDA's standards database.[1] In Europe, the standard was published under EN ISO 11135:2014 and may become harmonized in future updates of the harmonized standards lists (for the Directives 93/42/EEC and 90/385/EEC) published in the Official Journal of the European Community.

Medical device manufacturers should compare their current sterilization processes to the new standard requirements and generate a quality plan that includes any changes necessary for transitioning to the 2014 version.

The resulting rationale should support the need to either perform a re-validation or document that the current process is appropriate.

ISO 11135:2014 introduces various new requirements applicable to medical device manufacturers, suppliers of sterilization services, and healthcare facilities that sterilize disposable or reusable medical devices. Annex D superseded ISO 11135-2:2008 and is intended to explain the standard's requirements in common terms a non-expert can understand.

This paper outlines the EO sterilization principles, highlights the main new requirements, and discusses critical topics medical device manufacturers engaged in EO terminal sterilization should consider to comply with ISO 11135:2014.



The international standard ISO 11135:2014 and European standard EN ISO 11135:2014 are identical with the exception of annexes ZA and ZB, which relate respectively to corresponding elements of EN ISO 11135:2014, European Directive 90/385/EEC, and European Directive 93/42/EEC that are summarized in Table 1.

Table 1: Essential requirements addressed by EN ISO 11135:2014

	Essential Requirements from Directive 93/42/EEC	Essential Requirements from Directive 90/385/EEC
EN ISO 11135:2014	8.3 and 8.4	7

Source: Emergo, ISO 11135:2014 Annex ZB

Generality

As stated in the standard ISO 11135, sterilization is a validated process used to render a product free from viable microorganisms under a sterility assurance level.

To implement this process, a sterilizer is installed in a dedicated facility and the sterilization control equipment is located outside the room to appropriately and safely control the process according to defined parameters and requirements.

The sterilization may use various agents composed of either pure EO or mixtures with carbon dioxide or nitrogen. EO gas must be stored, handled, and used with precaution due to its toxicity, flammability, and explosive risk from 2.6% by volume in air.

The following steps make up the sterilization process:

- Preconditioning: achievement of levels of humidity and temperature before the load introduction into the chamber, ensuring a sterilization process without considering any initial environmental influences.
- Sterilization cycle: the usual EO sterilization process consists of the following phases:
    - Air removal: to avoid the risk of exceeding the safe EO limit by volume in air during the EO injection.
    - Chamber leak test.
    - Inert gas addition: to reduce any further issues with EO residues after sterilization.
    - Conditioning: achievement of defined levels of humidity and temperature, ensuring a level of moisture in the chamber.
    - EO injection.
    - Exposure.
    - EO removal: removal of gas under the explosive limit.
    - Flushing and air/inert gas admission: during the EO removal, multiple alternate admissions and evacuations of filtered air, inert gas or steam through the load and chamber to decrease the level of gas below the explosive limit by replacing the volume by the addition of inert gas (e.g. nitrogen).
    - Aeration: also known as degassing; placement of the load in a dedicated heated room to help the removal of EO residue.

The load configuration in the chamber can influence the heat distribution pattern of the product, humidity levels, EO gas penetration, and EO gas removal. The load configuration shall be designed to allow removal of air and penetration of heat, humidity, and EO during the sterilization process, as well as final removal of EO at the end of the process.

Process Characterization

Process characterization aims at defining the range of process variables needed to deliver the sterilization process safely. The ISO 11135 standard refers to the minimum of process variables to document in every phase of the sterilization process as illustrated in Table 2.

Table 2: Variables to consider for process characterization

Phase	Process variables associated with each phase
Pre-conditioning	Time, temperature, humidity, and transfer time
Sterilization cycle	Exposure time, temperature, humidity, EO concentration, and pressure
Aeration	Time and temperature

Source: Emergo, ISO 11135:2014 section 6.2

For a current EO sterilization process, the manufacturer should take care in their facilities or with their contract sterilization suppliers to check whether the process characterization is correctly established according to the variables defined in ISO 11135.

Though the variables are consistent between the former and new ISO 11135 standards, the implementation is more restrictive in the latest version.

Indeed, Annex D provides, per phase and sub phase, an exhaustive and detailed list of considerations around the variables to examine (see example of air removal sub phase in Table 3).

Table 3: Examples of variables identified in a Sub Phase according to ISO 11135

Phase	Sub phase	Variables to consider
Sterilization cycle	Air removal	Depth (ΔP or terminal pressure) of attainment of vacuum
		Rate (ΔP/time) of attainment of vacuum

Source: Emergo, ISO 11135:2014 Annex D section 6.2.4

Equipment Characterization

This phase of characterization consists of the establishment of equipment specifications to purchase the appropriate equipment suitable for the sterilization process and able to fulfill the requirements of ISO 11135.

There is no new significant difference between former and new ISO 11135 standards with the exception that equipment specifications must meet requirements related to installation services.

The guidance in Annex D also recommends that sterilization process equipment is able to detect and alert deviations to cycle parameter. This capability is intended to improve the implementation of corrective and preventive actions (CAPA) in a timely fashion.

Finally, the same annex provides a list of considerations or recommendations to take into account when establishing equipment specifications. Companies that sterilize shall review the current defined specifications to determine if all items of Annex D are addressed. As an example of items to review: “The system for admission of EO to the sterilizer should be equipped with a vaporizer to prevent liquid EO from being admitted to the sterilizer chamber.”

These updates directly affect the manufacturers (or their contract sterilization suppliers) who have access to sterilization equipment and who must purchase new equipment components or upgrade them according to the new ISO 11135 requirements.

Product and Process Definition

Product Definition

The product description aims at defining the product to be sterilized in terms of physical attributes, comparison with existing products used for validation (Process Challenge Device), intended use, design characteristics, raw material, defined Sterility Assurance Level (SAL), packaging, load configuration, and compatibility with EO. This characterization includes the assessment of product microbiological quality prior to validation and the assessment of product and packaging for safety, quality and performance following the application of the sterilization process.

The product description is the manufacturer's responsibility even though a third party could perform the activities of testing and/or sterilization validation.

The ISO 11135 standard states that device cleanliness and microbiological quality must be controlled to avoid compromising the sterilization effectiveness. Indeed, for reusable medical devices, the efficacy of cleaning and/or disinfecting processes carried out before the sterilization is to demonstrate according to ISO 15883 series for washer disinfectors. As well, for single use medical devices, the bioburden must be determined periodically according to ISO 11737-1[2] to control the device microbiological quality before the sterilization process occurs.

Process Definition

The process definition aims at establishing for a defined product's range of specifications for the sterilization process that may influence process efficacy. A process definition is related to a sterilization chamber that has been qualified (Installation Qualification and Operational Qualification or IQ and OQ), and the records support the implementation of process parameters on a Process Challenge Device (PCD). Biological indicators (BI) or sterility testing may be part of the process definition and must comply respectively with applicable ISO 11138-1[3] and ISO 11737-2[4] standards.

There is no significant difference between the former and new ISO 11135 in regards to process definition requirements.

Validation

The purpose of validation is to demonstrate that the defined sterilization process can be delivered effectively and reproducibly to the product within the sterilization load. Validation consists of a number of identified stages:

- Installation qualification (IQ) establishes that the sterilization equipment has been supplied and installed in accordance with specifications.
- Operational qualification (OQ) establishes the ability of the equipment to operate within the range of defined process parameters.
- Performance qualification (PQ) establishes that the equipment consistently operates, resulting in products that reproducibly meet the SAL.

The validation activities, PCD, load configurations, and product/process definitions must be recorded and the validation report must be reviewed and approved for acceptability. The report must include the EO process specifications; both the new and previous versions of the standard define the minimum specifications that must be part of the report. However, the new ISO 11135 references supplemental considerations for the stages of inert gas flushing and post-inert gas flushing (pressure and rate of vacuum attainment; pressure and rate of pressure attainment associated with inert/gas steam; number of repetition and the associated variations) as well as the conditioning stage (number of pulses/vacuum).

Installation Qualification

This phase involves checking that installed equipment complies with the specifications defined during the process and equipment characterization, as well as with applicable safety standards. The manufacturer must also define the operating procedures and instructions for the process to operate appropriately and safely (e.g. EO storage, instrumentation calibration, operation, etc.).

The new ISO 11135 includes in the IQ the services associated with the management of the equipment, such as outsourced maintenance, technical support, etc. Moreover, any changes made to the installed equipment must be assessed and documented as part of the design control for the impact on the design and process specifications.

Operational Qualification

The operational qualification phase consists of the calibration of all the instrumentation used for monitoring, controlling, indicating, or recording in order to demonstrate the capability of the equipment and ancillary system to deliver the operating ranges defined during the process definition. For instance, the operational qualification should document that the pressure for air admission can be achieved, or that the temperature sensor is correctly positioned in the chamber to measure the maximum temperature difference. Similarly, all the software systems, including ancillary equipment, must be tested in all fault conditions during OQ to demonstrate they operate correctly in worst-case conditions.

The new ISO 11135 does not significantly modify the requirements established by the former ISO 11135 in regards to the operational qualification.

Performance Qualification

Performance Qualification is a testing phase composed of two stages. The first stage, called microbiological qualification (MPQ), consists of achieving the specified SAL when the most critical parameters of the defined process that kill the least microorganisms on the PCD are applied, and when the exposure time, the key parameter for lethality, has been reduced. The second stage, called physical performance qualification (PPQ), consists of checking that critical process specifications are met everywhere in the sterilization load throughout the duration of the cycle and the sterilization process is reproducible. For instance, is the level of humidity within the acceptable range established by the process definition throughout the duration of the pre-conditioning phase?

The new ISO 11135 does not significantly modify the requirements established by the former ISO 11135 in regards to performance qualification.

Microbiological Qualification (MPQ)

The MPQ is performed to establish the effectiveness of the sterilization process in a specific sterilization chamber for a load configuration of PCD. There are two methods that may be used to determine the cycle lethality: overkill approach or biological indicator (BI)/bioburden approach.

The overkill approach is a conservative method and consists of either:

- Three (3) runs of sterilization for a half-cycle exposure time that must kill all the BI (with population at least at 10^6) and a short duration cycle for the validation of BI recovery technique, or
- Various numbers of cycles depending on the method used for BI recovery, which determine the routine process parameters delivering 12 Spore Log Reduction (SLR) of the BI by extrapolation of the probability of a surviving microorganism.

The BI/Bioburden approach is to establish the level of product bioburden and choose a BI more resistant than the product bioburden level. The BI are placed at critical locations and the sterilization cycle is run at graded or single exposure times depending on the method used for BI recovery. The objective is to establish or extrapolate the rate of inactivation of the sterilization cycle.

The conditions for BI recovery by direct enumeration or fraction negative methods are referred to in the reference standard ISO 14161[5].

The new ISO 11135 specifies that microorganisms may be observed in the internal PCDs if the calculated SAL meets the specified value. Indeed, when the log reduction obtained for a half-cycle exposure time ensures that 6 log reduction has been obtained for a full cycle, the number of microorganisms present in the internal PCD may be acceptable.

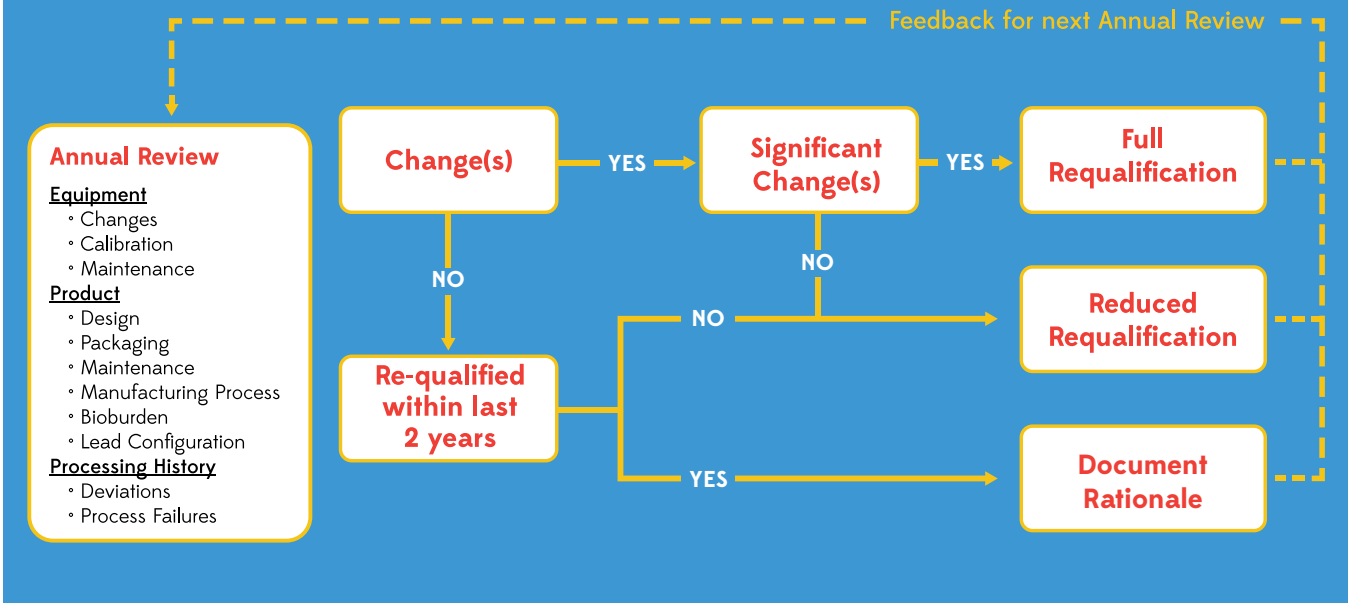
Physical performance qualification (PPQ)

The PPQ is formally documented by three consecutive runs of the sterilization process in which all acceptance criteria are met. The PPQ and MPQ may be performed during the same runs of sterilization, but in this case an additional run of sterilization must be conducted with the full routine process parameters (commonly referred to as a full cycle). Both former and new versions of ISO 11135 detail the minimum requirements to be met during PPQ, such as the temperature of sterilization load during aeration. However, the new version adds three new considerations to assure conformance during validation and routine sterilization activities:

- When entering in the sterilization process, the minimum product temperature.
- The chamber humidity (for parametric release).
- Increase of pressure and EO quantity/concentration in the sterilization chamber (for parametric release).

Through the new ISO 11135, an annual review of sterilization process shall be carried out according to the following excerpt of the standard:

Figure 1: Requalification decision tree according to ISO 11135:2014



Source: ISO 11135:2014 Annex D section 12.3.3

A full requalification involves PPQ and MPQ; a reduced requalification involves at least one fractional or half cycle exposure including load temperature and humidity measurements.

The purpose is to annually and appropriately confirm the product SAL (e.g. resistance or level of bioburden) through a review of IQ/OQ/PQ for the validated sterilization process. The review and further activities (microbiological studies) shall be documented.

The calibration status of the control and monitoring equipment must be confirmed. The specified equipment used shall be periodically reviewed regarding their performances, temperature and humidity profiles (preconditioning area, aeration area, chamber, etc.) and the change(s) applied. The review must confirm the sterilized products have not been significantly changed (e.g. in terms of design, manufacturing, packaging material, suppliers, PCD, etc.) as that could affect the product sterility or the process to operate within the specifications.

Change and Equivalence Assessments

Change Assessment

Any change that is applied to a manufacturing process, product, sterilization equipment, or other process, as well as sterilization load changes must be evaluated by the manufacturer to determine the qualified sterilization process effectiveness.

The expected results of the evaluation must match up at least on the PCD acceptance and bioburden confirmation.

Equivalence Assessment

AAMI TIR28 states: "it does not require that the equipment be physically identical and even if the parameters delivered by the equipment are not statistically identical, the processes delivered can still be equivalent if they are all capable of running the process within the defined, validated process limits." The process equivalence may reduce the number of tests when many types of equipment may be used for the same validated process.

A rationale of equivalence may be documented to evaluate:

- Any additional sterilization equipment introduced in the current validation process
- Any additional products introduced in the current validation process

When qualified (IQ and OQ) sterilization equipment are able to deliver the same process parameters, the equipment may be used if the performance qualification has been successfully performed:

- as with the original equipment in the same chamber, or
- using a reduced MPQ (with the required level of microbiological lethality achieved) and a PPQ that ensures that the process parameters are still delivered to the products within the defined tolerances.

A product may be added to a validated process if documented as equivalent to an existing qualified product or internal PCD. The assessment includes a technical review considering product safety, quality and performance (e.g. Biocompatibility, EO residue) with the final decision for inclusion.

Routine Monitoring, Control and Product Release

The manufacturer is responsible for routine product release, and must ensure that the validated and specified sterilization process has been delivered to every run of products.

The responsibility is to maintain sufficient records supporting claims that the sterilization process specifications have been met.

In routine sterilization activities, the monitoring consists of checking the sterilization process parameters and using biological indicators to attest the products have been exposed to the EO gas.

The new ISO 11135 details all the parameters to record and check during product release. (e.g. minimum temperature of product entering the sterilization process or time, temperature, pressure changes during aeration, etc.). In particular, the new ISO 11135 adds the following requirements to consider from the previous version:

- EO injection time,
- Inert gas injection if used,
- Time taken to evacuate the chamber,
- Time and pressure changes during post-exposure flushing.

Moreover, supplemental tests such as endotoxin or EO residuals may be required to release the sterilization load depending on the type of product, exposure of the product to humans, and the risk classification of the finished medical device.

The new ISO 11135 standard now provides details regarding a load that does not comply with the acceptance criteria for concession or when a manufacturer wishes to release the products issued from validation into the market.

When the load does not meet the acceptance criteria, the manufacturer shall investigate the deficiencies observed to avoid its recurrence as part of the corrective action plan. Another circumstance may be a new qualification shall be implemented when equipment has been repaired through unscheduled maintenance before being used again for the sterilization process.

Considering the products used during validation, the manufacturer may release the load after:

- Having accepted the product / packaging functionality and residual EO following repeated exposures
- Ensuring the products from MPQ have undergone a full exposure to the specified sterilization process

Parametric Release

Parametric release is a product release based on a documented review of records that must ensure that the essential physical sterilization process parameters are delivered within the specifications established during the validation. The product release is consequently not related to biological indicator or PCD testing.

When this alternative release process is used, supplemental requirements must be considered during sterilization validation to establish the specifications that will be verified in routine.

As well, specific sterilization equipment must be used in the sterilization process to meet the ISO 11135 requirements, such as analytical instrumentation for the direct analysis (e.g. electronic sensors, gas chromatography or spectroscopic methods) of humidity during conditioning and EO concentration during EO exposure time.

Parametric release consists of checking the usual sterilization process parameters and confirming that they meet the sterilization process specifications; specifically for parametric release, the checking must also consider:

- The temperature in the chamber throughout the sterilization process at two locations
- The chamber humidity during conditioning by direct analysis
- The EO concentration using analytical method during at least the first and last portions of EO exposure to verify that required conditions are met.

Single Lot Release

The new ISO 11135 defines in Annex E the requirements applied to the single lot release for the purpose of research and development or medical devices intended to be used for clinical trials. Therefore, companies do not have to go through a full sterilization validation when they decide to release a single batch of products for use in a clinical trial or in research.

If the packaged product can be assigned to a product family, the sterilization process will be considered as validated through a documented assessment of equivalence (see Equivalence Assessment section).

Otherwise, the sterilization process approval consists in three main stages:

- Determination of average bioburden after selection of samples from the batch to perform testing according to 11737-1 standard,
- Exposition of sterilization load, that includes internal PCD with BI, at minimum process parameters for a SAL<10-1, and
- Exposition of the same sterilization load (with new internal PCD with BI) to the nominal process parameters.

Note: an aeration period is performed between both sterilization stages

At the end of the first stage, product samples are taken at locations where sterilizing conditions are most difficult to achieve. The samples as well as internal PCD (and external PCD if used) will be subjected to sterility testing according to the ISO 11737-2[6] standard. Afterwards, at the end of the second stage of sterilization, the new internal PCD replacing the first one in the sterilization load will be tested (as well as new external PCDs if used) according to ISO 11737-2 standard.

Finally, the lot will be released under a specific detailed list of conditions and including:

- Sterility tests are negative for external PCDs (if used) and internal PCDs that have been exposed to the fractional sterilization cycle and the full sterilization cycle,
- Sterility tests are negative for product samples taken after exposition to the fractional sterilization cycle,
- Product functionality, stability and package integrity comply with requirements after exposure to the full sterilization cycle,
- Confirmation that level of EO residue complies with the requirements of ISO 10993-7[7] after the fractional and the full sterilization cycles.

Summary of Changes

The following Table 4 presents an overview of the main differences between ISO 11135:2014 and ISO 11135-1:2007.

Table 4: Summary of changes

Activities	Main changes in ISO 11135:2014
Process characterization	• Exhaustive list of sterilization process variables to consider
Equipment specifications	• Additional requirements related to installation services • Additional equipment to detect and alert deviations to cycle parameters • Additional considerations in Annex D when establishing equipment specifications
Sterilization process validation	• Additional variables to consider during stages of inert gas flushing, post-inert gas flushing and conditioning • Inclusion in IQ of the services associated with equipment management (maintenance, technical support) • Additional variables to consider during the PPQ (e.g. temperature of product entering in sterilization process)
Requalification	• Annual review of sterilization process to implement
Product release	• Exhaustive list of parameters to record and check for product release with additional considerations (e.g. time taken to evacuate the chamber)
Change Assessment	• Confirmation of the PCD and bioburden acceptance as well as the effectiveness of sterilization process, for any changes related to the product or manufacturing processes
Product and process equivalence	• New section • Definition of requirements to release devices that are not compliant to specified criteria or coming from validation
Single lot release	• New section for batch used in research or for clinical trials

Source: Emergo

Conclusion

As discussed in the introduction, compliance with the ISO 11135:2014 standard is more and more often required worldwide. Therefore, manufacturers must determine the standard's impact on their current sterilization processes to establish a Quality Plan, which may directly affect:

- The sterilization equipment (e.g. detection equipment for deviations to cycle parameters, sterilizer with vaporizer)
- The sterilization process that must be under control according to a detailed list of variables (e.g. ΔP for EO injection, EO injection time and terminal pressure of EO injection phase)
- The sterilization validation, through the capability of new equipment or the considerations of new sterilization process variables, etc.

The action plan should be defined, implemented, and show whether a re-validation is necessary, or at least should state there is no impact.

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Manufacturers must review henceforth their sterilization processes annually to document that the equipment used and product SAL are appropriate, as well as to show that the changes applied to products and processes do not affect the sterility and the sterilization process to operate within the specifications.

Additionally, all changes that may affect product or the manufacturing processes must be assessed in regards to bioburden confirmation and PCD acceptance.

Finally, the new ISO 11135 standard introduces an Annex E related to single-lot releases applied for the purpose of research or for clinical investigation, consequently reducing the previous manufacturer uncertainties in regards to these specific situations.

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6 Sterilization of medical devices -- Microbiological methods -- Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process
7 Biological evaluation of medical devices -- Part 7: Ethylene oxide sterilization residuals