Innovative solutions for sterile medical devices

Use of non-standard terminal sterilization modalities

bsi.

By Royal Charter

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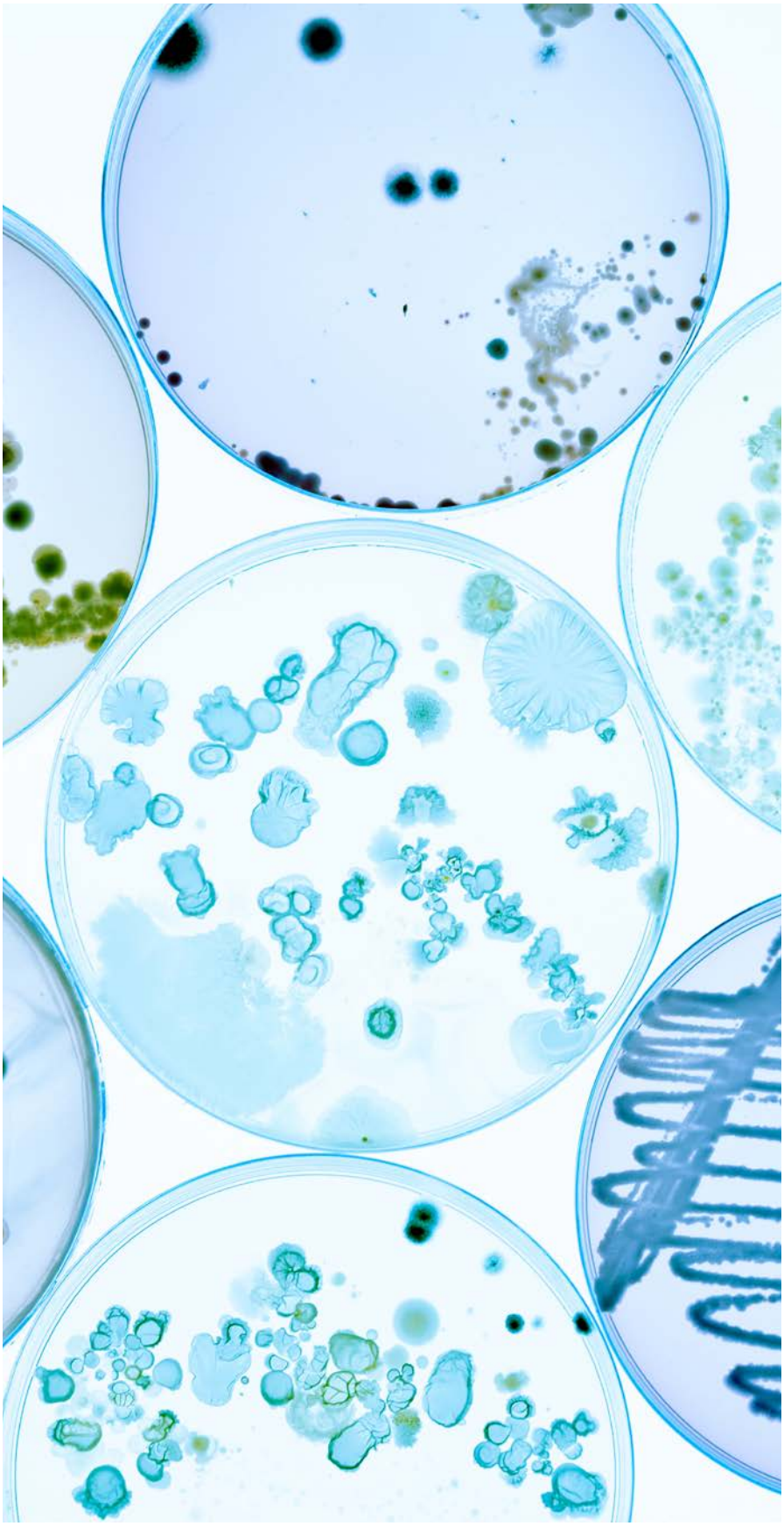


Overview

BSI Netherlands Notified Body is now ready to support the strategic goals of the medical device industry as it seeks to introduce and incorporate new technologies and drive sustainability. Concerns over sterilization capacity, availability of natural resources, public concerns over environmental exposure and safety concerns over individual exposure have grown over the past decade and this has led to exploration into alternative sterilization technologies. Regulatory agencies are also responding to public concerns regarding safety and environment.

On July 15, 2019, the US Food and Drug Administration (FDA) announced two public innovation challenges:

- **Challenge 1- Identify new sterilization methods and technologies:** the goal of this challenge is to encourage the development of new approaches to device sterilization methods or technologies for medical devices that do not rely on ethylene oxide.
- **Challenge 2 - Reduce ethylene oxide emissions:** the goal of this challenge is to develop strategies or technologies to reduce emissions to as close to zero as possible from the ethylene oxide sterilization process.

In 2019, ISO 10993-7 was also updated to consider patient size and special populations when calculating ethylene oxide residue limits. Lower residue thresholds apply, for example, to medical devices for neonates and children.

The US Environmental Protection Agency (EPA) has proposed amendments to the National Emission Standards for Hazardous Air Pollutants (NESHAP) for the Commercial Sterilization Facilities source category. Once these amendments are released, it is currently proposed that the medical device industry will have an 18-month transition period within which to comply.

In the absence of current regulations, the closure of sterilization facilities continues as a direct result of public concern, media coverage and increasing lawsuits. On occasion, closure of these sites has been at short notice, which increases the impact and strain on the medical device industry.

In addition to these challenges being faced by the use of ethylene oxide, the other most prevalent sterilization modality, gamma radiation, is not without its own challenges. Supply of cobalt-60 is limited to a number of countries and requires regular replenishment. Therefore irradiation technologies arising from electron beam and x-ray are gathering traction as they do not rely on a supply of this limited natural resource.

Introduction

This white paper summarizes how the use of a non-standard sterilization technology in the manufacture of medical devices has both benefits and risks that need to be considered in relation to the overall safety and efficacy of devices. Non-standard methods of sterilization in this context are identified as modalities whose use is not published in a dedicated international standard and therefore primarily relies on the approach prescribed in ISO 14937 as a route to conformity for the sterilization aspects of a medical device. The demonstration of sterilization effectiveness will be the primary challenge when considering a non-standard modality and these will invariably attract greater scrutiny by regulators. Those developed on a bench top or within a laboratory may encounter obstacles during the process of scaling up to industrial capacity and may remain limited in scale but suitable for applications involving novel products or materials. Despite these factors, there are numerous potential benefits including less harmful residues, increased operational safety and greater security of the supply chain. Not all Certification Bodies, Approved Bodies or Notified Bodies will have the capability to support their clients' requests for approval to utilize non-standard sterilization processes due to restrictions within their own scopes. BSI Netherlands Notified Body now carries a scope of accreditation that includes a broad range of sterilization modalities, including many non-standard sterilization methods.

There are many terminal sterilization modalities that are specifically described in international standards. These methods have had long and extensive use such that industry and regulators have been able to determine, document and agree requirements that ensure that sterilization can be validated and implemented to deliver a defined level of sterility assurance. Currently, ISO standards have been published for ethylene oxide, radiation (i.e., gamma, x-ray and electron beam), moist heat, dry heat, low temperature steam and formaldehyde, and most recently, vaporized hydrogen peroxide. These published standards have a common approach and contain specified scopes of application with defined limitations.

Non-standard sterilization modalities

As the medical device industry continues to innovate, available sterilization technologies need to evolve to keep pace. New methods of terminal sterilization are constantly in development. However in some instances, the technology is not new but has not yet gained widespread acceptance or use by medical device manufacturers. Equipment originally designed for alternative uses such as decontamination, or other industries (e.g., veterinary or food) could be obtained by device manufacturers and repurposed for device sterilization. There may be cases where previous research into new non-standard sterilization modalities was discontinued due to internal constraints such as financial pressures or competing priorities. These discontinued projects may see a renewed focus on their development and could still prove to be an effective solution for device sterilization. The desire for new solutions is currently driven by availability and security of supply, and concerns for patient and environmental exposure to sterilants and their residues.

Emerging factors driving innovation:

Materials

- Novel device materials
- Improving shelf life
- Improving operational lifetime
- Better clinical performance
- Biocompatibility
- Natural resource limitations

Environment and Sustainability

- Reducing carbon use, energy use and waste
- Low/no emissions
- Minimizing packaging
- Exemption from licensing burdens
- Regulatory restrictions

Development and validation requirements

Attention must be paid to the scope and exclusions of the dedicated standards when approaching the development and validation requirements. For example hydrogen peroxide, when used with other agents is not included in the scope of ISO 22441. Likewise, ethylene oxide when used as a sterilant in a flexible chamber is excluded from the scope of ISO 11135. In such cases, where the specific approach to a standard sterilization causes it to be excluded from its dedicated standard, then the ISO 14937 standard applies.

The ISO 14937 standard gives a framework for the development, validation, and routine use of non-standard sterilization modalities. It includes additional considerations when compared to dedicated sterilization standards such as characterization of both the sterilization agent and the sterilization process. Development of such aspects usually falls outside the expertise of medical device manufacturers and tends to be the most challenging aspect when developing a new sterilization cycle under ISO 14937.

Characterization aspects are already addressed for standard modalities because the processes and sterilization agents have been studied and documented for many years. This is acknowledged within some sterilization standards, for example clause 5.2 of ISO 11137-1 states the following:

"The inactivation of microorganisms by radiation and the use of radiation in sterilization processes have been comprehensively documented in the literature. This literature provides knowledge of the manner in which the process variables affect microbial inactivation. Reference to these general studies on microbial inactivation is not required by this part of ISO 11137."

This is in contrast with the normative sections of ISO 14937, clause 5, which specifies the need to demonstrate microbicidal effectiveness, material compatibility and safety:

"The sterilizing agent shall be specified. The specification shall include, if appropriate, conditions of storage of the sterilizing agent to maintain the sterilizing agent within its specification for the duration of the stated shelf life."

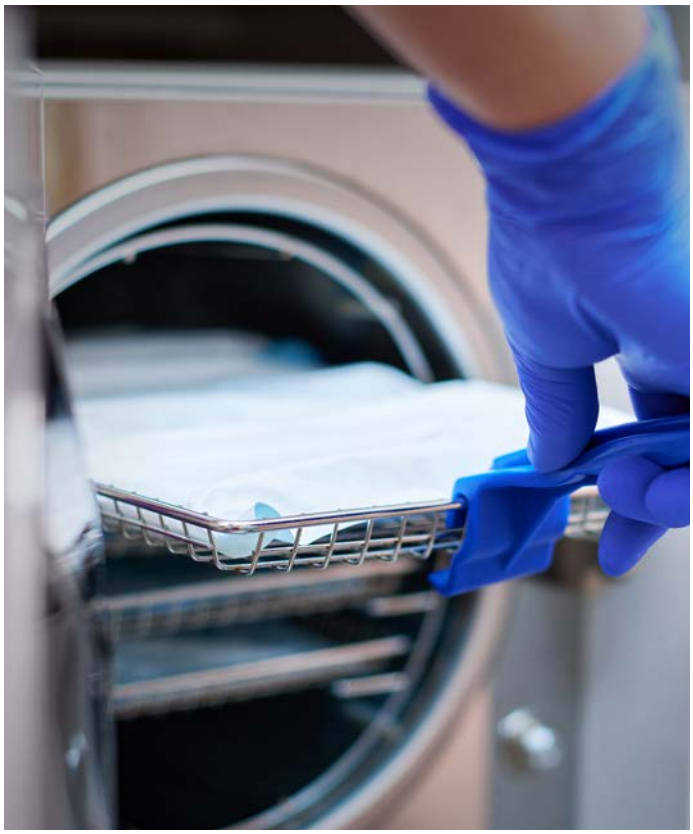
The annexes of ISO 14937 present further guidance on demonstrating microbicidal effectiveness. A medical device manufacturer must be able to demonstrate the suitability and effectiveness of the sterilant. Initial development activities will be needed to demonstrate the effectiveness and efficacy of the sterilization agent in combination with the sterilization equipment prior to commencing the validation activities.

The requirement for characterization cannot be bypassed, even in the case of a manufacturer who purchases a commercially available piece of equipment designed and intended to perform non-standard sterilization. Manufacturers are still required to demonstrate the characterization and its relevance to their medical device. This may become even more complex if the sterilization equipment manufacturer regards their own development and validation methods as proprietary.

Supplies of equipment and spare parts might present difficulties if the process does not achieve widespread use. The expectation of BSI Netherlands Notified Body is that manufacturers address both the normative and informative when demonstrating method suitability, repeatability, and reproducibility of their non-standard sterilization processes. Although guidance is, by definition, not mandatory any guidance that can be applied should be applied in order to ensure most effective coverage of all requirements. Regulatory questions will arise where guidance offered in the informative sections of ISO 14937 has not been considered or does not have a suitable justification for omission or non-applicability.

Characterization of the sterilization agent requires a demonstration of lethality against a range of organisms, represented by more than the commonly used laboratory strains. Suggested challenge organisms are given in Annex A of ISO 14937. Biological indicators are specific to sterilization modalities and any non-standard process cannot simply adopt an off-the-shelf biological indicator without verification. The selected indicator organism needs to be shown to be more resistant than the natural bioburden on the products but also sufficiently resistant to be used as an indicator. The sterilant mechanism of action must be understood to ensure that any inhibitory conditions might be identified and controlled. Factors affecting sterilant penetration in the load and microbial inactivation during the process also need to be considered to ensure that all parts of the devices are sterilized. Development testing of the sterilant should look for extremes and test the limits of application to gain understanding of when and how a process will fail.

The results of reduced exposures of test organisms can be used to predict the point at which the desired sterility assurance level (SAL) is obtained. Extrapolation cannot be assumed, and numerous treatments can be required to confirm that a predictable SAL can be calculated. In other words, moving too swiftly to a



half-cycle approach is not appropriate without first showing that fractional results are representative and that subsequent half-cycles can be used to generate a validated sterilization process.

A sterilizing agent will generally interact with and affect the materials of the product. Robust testing to demonstrate the limits of these effects must be documented. Product (including packaging) compatibility should be established such that the lifetime of the device is supported. Published information on product materials might support the chemical stability in addition to direct testing appropriate to the sterilization process. For example, a permanent orthopaedic implant must retain its structural properties for many years, and the potential for processed materials to react in unexpected ways within the body over time should be considered.

The equipment and processes necessary for control of the sterilization modality within its limits of application must be identified and justified since different sterilization agents will have different requirements.

For example, consider a process involving an electrically activated gas where small variations in activation level can have a major effect on lethality. Tighter control specifications of the activation energy would need to be applied, including increased precision of the control, and monitoring instrumentation.

Only once the sterilizing agent, equipment, and process are defined through development testing, qualification and process validation can proceed. During the validation stages, the selection of protocol methods requires consideration and justification to ensure that the appropriate process variables are in control. The decisions on how to demonstrate that equipment is operating and performing correctly are with the device manufacturer.

Regulatory assessment of change of sterilization modality

Manufacturers will look at non-standard technologies to gain benefit or mitigate existing risks but should be aware of issues that may arise in the solutions they select. Non-standard methods of sterilization will require additional resources to produce or obtain the data that confirms the safety and effectiveness of the modality. Additional time will also be required to present this information for regulatory approval.

International Standards represent state of the art and are consensus documents that specify minimum requirements for compliance. Compliance with the published standards provides the structure that allows a streamlined approach to achieve certification. Where ISO 14937 is applied, the Assessment Body cannot presume many aspects relating to the method effectiveness and must question the development of the sterilization modality. Additional time will be applied to ensure an effective assessment. The risks and costs related to regulatory or third party approval could be minimized if clear responses can be provided in response to regulatory questions.

Conclusion

Despite the additional workload and regulatory scrutiny, new methods of sterilization are an option that should be considered, developed, and implemented. Risks and regulatory pressures associated with the traditional modalities exist and although it takes time for the acceptance of other approaches, these non-standard and in some cases novel sterilization modalities are necessary to provide the sustainable and cost-effective solutions of the future. On 8 March 2023, BSI Netherlands Notified Body's scopes of designation under MDR and IVDR were expanded to include six new sterilization modalities. We are the first Notified Body to achieve this designation to allow CE marked devices using such technologies onto the EU market.

BSI Accreditations and Designations

BSI is also accredited to ISO13485 by RvA for the assessment of sterilization methods other than specified above, including applicable quality management system requirements within ISO 14937.

Annex to declaration of accreditation (scope of accreditation):

- Normative document - EN ISO/IEC 17021-1:2015
- Registration number of BSI Netherlands Notified Body - C 122

BSI Netherlands Notified Body (2797) scopes include the following range of technologies under Regulation (EU) 2017/745 on medical devices and Regulation (EU) 2017/746 on in vitro diagnostic medical devices which was recently expanded to include:

- Sterilization with hydrogen peroxide and ozone
- Sterilization with peracetic acid
- Ethylene oxide gas sterilization (EOG) in flexible chambers
- Sterilization with supercritical carbon dioxide
- Sterilization with nitrogen dioxide
- Sterilization with chlorine dioxide

Click here for NANDO designation scope

Standards

Standards	Title
ISO 11135	Sterilization of health-care products - Ethylene oxide - Requirements for the 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 17665-1	Sterilization of health care products - Moist heat - Requirements for the development, validation and routine control of a sterilization process for medical devices
ISO 14937	Sterilization of health care products. General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices
ISO 20857	Sterilization of health care products - Dry heat - Requirements for development, validation and routine control of a sterilization process for medical devices
ISO 22441	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
ISO 25424	Sterilization of health care products - Low temperature steam and formaldehyde - Requirements for development, validation and routine control of a sterilization process for medical devices

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