Sterile Manufacturing Quality Control Methods in the Medical Products Industry

Toma Stulgė[1], Rūta Rimašauskienė[1*]
Kaunas University of Technology, Faculty of Mechanical Engineering and Design, Kaunas, Lithuania
toma.gagyte@ktu.edu, ruta.rimasauskiene@ktu.lt

Abstract: *Manufacturing of medical products is a very wide market. Many steps must be taken to ensure that produced product is sterile and safe and efficient to use for the customer. All manufacturing system from production floor to the type of sterilization must comply with required standards and regulatory. Every step of introducing new product to the production to routine production itself must be well documented and justified to be able to release the product to the market for human consumption. This paper presents information of production area requirements for medical devices, sterilization methods and sterilization indicators, briefly overlooks the quality control of such processes and the effectiveness of it.*
Keywords*: STERILE, MANUFACTURING, QUALITY CONTROL, MEDICAL PRODUCTS, STERILIZATION*

1. Introduction

The importance of quality control and inspection in manufacturing of sterile medical devices is exceptionally high. Stardartized procedures and quality control methods must be incorporated into routine production and followed strictly to ensure the best quality product will reach the customer and complaint level for the company will be as low as possible. Sterile medical devices should be sterile because these products are going to be infused directly into the bloodstream or body tissues [1].

Many steps must be taken to produce the sterile medical device. Starting from the qualified production area, validated and verified production processes, appropriate sterilization methods, succesfully passed audits and maintened required certification level. Many standards and requiraments must be fulfilled before succesfuly releasing the product to the market and, for example, ISO 13485 is one the most basic and most commom standard that medical devices manufacturer must follow. This standard basically specifies all requiraments for the Quality Management System for the manufacturer. The manufacturer of medical devices must demonstrate the ability to provide such medical devices and services that meets regulatory and customer requiraments. Besides compliance to ISO 13485, medical devices manufacturers has to comply with many more regulations and guidelines instituted by the FDA, ISPE, EMA, MHRA, and ICH, emphasizing good manufacturing practice and inspection requiraments in the manufacturing of medicinal products [2]. Sam A. Hout studies sterile manufacturing requiraments and fundamentals of aseptic techniques, quality by design, risk assesment, and management in support of sterile operations application [2] in the book "Sterile manufacturing. Regulations, processes, and guidelines".

Country/region	Standards/regulations	Conformity assessment
Australia	ISO13485 or EN46001[a] ISO13488 or EN46002[a]	Government and third party
Canada	ISO13485, ISO13488	Third party
European Union	EN46001[a] or ISO13485 EN46002[a] or ISO13488	Third party
Japan	GMP #40 ordinance GMPI #63 ordinance QS Standard for medical devices #1128 notice	Government
United States	QS (21 CFR part 820)	Government

Fig. 1 *Quality standards [3]*

The word "sterile" usually associates with the meaning that products or devices do not contain any viable pathogens, such as viruses, bacteria, fungi, and other living forms.

Neither visually nor by other means used nowadays, it is possible to quickly and without special research methods determine that one or another product is certainly "sterile". Nowadays, the term "sterile products" is understood to mean that these products or devices have been manufactured and prepared in appropriate ways, in accordance with strict rules and requirements. The necessary measures to ensure quality were used throughout the process, the process itself was controlled, and the results of the process and its control were documented. The concept also includes that the personnel involved in the processes have the necessary qualifications and are properly trained. The overall requirements for sterility are very nicely describe in Medical Device Directive 93/42/EEC points 8.3 – 8.7 and point 13.

The goal of sterile product is usually reached by sterilization or irradiation processes. Sterilization processes are carefully chosen for every type of the product or device as it can have a huge influence on product functionality and safety to the end user. These processes are expected to change used plastic [4], elastomer or other materials properties. Laurence W. McKeen investigates the effect of different sterilization methods on plastics and elastomers. Also, dozens of sterilization methods are reviewed in a very informative and simple way in the book "The Effect of Sterilization on Plastics and Elastomers" chapter 1. Medical devices manufacturers not only carefully choose the sterilization supplier, but also monitors closely the whole process. To ensure that sterilization process is completed successfully sterilization indicators are used widely across the industry. These indicators are used to identify that the procedure used for sterilization is completed and to avoid any confusion [5]. Shruti Moondra reviews the application of different types of sterilization indicators in the book "Sterilization of pharmaceuticals".

Cleanrooms and controlled production environment are a big part of medical devices, especially, sterile medical devices or pharmaceuticals production. The cleanroom environment has many potential sources of contamination, including: operators, equipment, structures, and any surface that can create particles via friction, heat, exhaust, outgassing, and static electricity charge [6]. During active production, millions of particles are generated into the environment. Associates that performs everyday activities in such production areas are considered to be one of the biggest contamination sources. This is the reason why the garment for operators and other personnel [6] must not be comfortable to work, but also be validated and monitored closely. Shih-Cheng Hu and Angus Shiue investigates the importance of validation, testing, penetration and application of the personnel factor for the garment used cleanrooms [6].

In this paper, production area requirements will be reviewed, as also the types of sterilization methods and indicators types. The quality control and effectiveness of sterilization process will be briefly overlooked in chapters 3.1 and 3.2.

2. Production area of sterile medical devices

Sterile medical devices are usually produced in cleanrooms, where environment is controlled. The product itself is usually not sterile immediately after production, but the bioburden level on the surface of such kind devices is significantly lower in comparison with normal production. Cleanrooms are frequently used not only for medical devices or pharmaceuticals production, but also for electronic, micro schemes or anything else that require low viable and non-viable particles concentration in the air.

Air filtration and overpressure are used to lower the particle and microorganism concentration presence in the environment, where production process is ongoing. Overpressure prevents air ingress

into the cleanroom, in this way when personnel is entering the room the particles from the outside does not flow into the room. The air is supplied through HEPA filters and high number of air changes per hour is kept. The biggest contamination in cleanrooms is considered to be people and materials as, in example, skin of a human sheds according the speed of its movement (Fig. 2).

Fig. 2 *Contamination from people [7]*

In the companies where cleanrooms are in operation special procedures are usually in place. Most manufacturers have established cleaning and disinfection procedures, gowning and behavior procedures, environmental monitoring programs, special personnel training programs, pressure monitoring instructions. For cleaning such production areas only approved and appropriate cleaning agents must be used, alternating them between to reduce the risk to develop bacterial resistance. The process of the cleaning must be validated to ensure its effectiveness.

Cleanrooms itself are classified into classes according the airborne particulate cleanliness per ISO 14644-1 standard (Fig. 3)

Table 1 — Selected airborne particulate cleanliness classes for cleanrooms and clean zones

ISO classification number (*N*)	Maximum concentration limits (particles/m³ of air) for particles equal to and larger than the considered sizes shown below (concentration limits are calculated in accordance with equation (1) in 3.2)					
	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1 µm	5 µm
ISO Class 1	10	2				
ISO Class 2	100	24	10	4		
ISO Class 3	1 000	237	102	35	8	
ISO Class 4	10 000	2 370	1 020	352	83	
ISO Class 5	100 000	23 700	10 200	3 520	832	29
ISO Class 6	1 000 000	237 000	102 000	35 200	8 320	293
ISO Class 7				352 000	83 200	2 930
ISO Class 8				3 520 000	832 000	29 300
ISO Class 9				35 200 000	8 320 000	293 000

NOTE Uncertainties related to the measurement process require that concentration data with no more than three significant figures be used in determining the classification level

Fig. 3 *Cleanroom classification [8]*

Before starting normal production, such area must be validated and regularly re-qualificated. Cleanrooms that is classified as 5 class or higher must be re-qualificated to demonstrate compliance with particle concentration limits every 6 months as the lower classes every 12 months. Routine environmental monitoring should be completed to define the limit values for alert and action limits. During such monitoring the room is usually at operation conditions and it must be documented what type of products were produced during testing, number of operating machines and personnel in the room. Microbiological analysis of such monitoring and identification of microorganisms can reveal the true origin of the contamination (air, material, water or people). Different sampling methods can be used to determine the contamination (Fig. 4).

Active air sampling	Passive air sampling (settle plates)	Surface sampling	Hand sampling	Garment sampling
Production, at operation, before starting the production	Indicate particles contamination on the product	Production – NOT on critical points within machine operation	Any time, after sampling disinfection!	Always before the texile garments are changed – before being washed
Dressing room – right after change, when no people are present	Dressing room – during the change	Dressing room – contact plates at/after change, different sampling points	Swabs or contact plates, gloves print	Swabs or contact plates - hands, armpit

AIR: passive or active sampling
PEOPLE: hand swabs, contact plates, clothes
SURFACES: surface swabs, contact plates (RODAC)

Materials & Products: bioburden acc. to documented control plan

Fig. 4 *Sampling methods*

3. Sterilization methods and indicators

Many medical devices and products require sterilization to ensure that they are effective and safe for customer use. Sterility is therefore a critical quality attribute and is essential [9] for these products. Medical device only can be sterile or non-sterile, no partial sterility is impossible. Sterilization of medical devices and products is performed in several different techniques. Nowadays mostly used techniques are these:

- Saturated water vapor sterilization;
- Sterilization with Ethylene Oxide (E.O.) gas;
- Sterilization with low temperature steam and formaldehyde;
- Sterilization with hydrogen peroxide plasma;
- Gamma sterilization;
- Sterilization with dry hot air.

For the control of effectiveness of these sterilization techniques indicators are most widely used. To date, there is no universal indicator of sterilization, which could provide control of the sterilization effectiveness for all types of equipment [10]. Those indicators could be chemical, biological or different data loggers.

The evaluation of chemical indicators (CI) is based on clearly visible discoloration/change of colour after the sterilization cycle is over. But the chemical indicator's colour change only shows that the conditions where CI was positioned were what the indicator was designed to indicate. Therefore, only part of CI are used to evaluate the sterilization process. The possibility of correctly evaluating the effectiveness of sterilization depends on proper selection of indicators and the interpretation of their readings. Unfortunately, none CI could show whether the sterilization was truly effective.

Biological indicators (BI) are the only indicators that provide reliable assessment of the efficiency of the sterilization process. They consist of a culture of bacteria that are highly resistant to the sterilization conditions under particular study. Different BI with different cultures of bacteria is used for every sterilization technique. To acknowledge that sterilized device or product is suitable for use after the sterilization process where BI were used could only be done after the results of BI evaluation have been received. The process of evaluating the readings of BI could take up to 48 – 72 hours.

Data loggers, digital devices that record the physical data of the sterilization process, on the other hand, are relatively new way to control and evaluate the sterilization process. Firstly, the recording of process data (parametric control), was introduced in the industry. Unlike chemical indicators or biological indicators, parametric control provides much more information about the course of the cycle, the sterilization conditions achieved and the duration of the cycle. These loggers can also provide (and provides) information about preparation for sterilization, such as removal of air from the chamber, duration and number of preparation stages for sterilization, etc.. The application of the method in industry has

brought tangible benefits to consumers and significantly increased reliability of sterilized products. After starting using this control technique manufacturers have reduced the risk of placing improperly sterilized products on the market and dispensed the huge quantities of CIs used so far. The application of parametric control resulted in lower product costs and cost to consumers.

3.1. Sterilization process quality control

Quality control methods calls for effective inspection procedures, but product testing may not always be adequate [11] for sterilization process control. The variation of the sterilized product testing methods brings the uncertainty while evaluating results. The most used classical methods of microbiological testing as quality control for sterilized products or devices may not always be the most suitable choice. Results of microbiological testing may show the capabilities of laboratory, its personnel and procedures than sterilization effectiveness itself. For radiation sterilization (gamma sterilization, e-beam sterilization) simple dosimetry may be the key. Since standardized dosimetry is fairly simple, reliable, and reproducible, there is a trend towards using this method for assuring safe product release [11]. In Fig. 5 number of the applications of irradiation dosimetry can be seen.

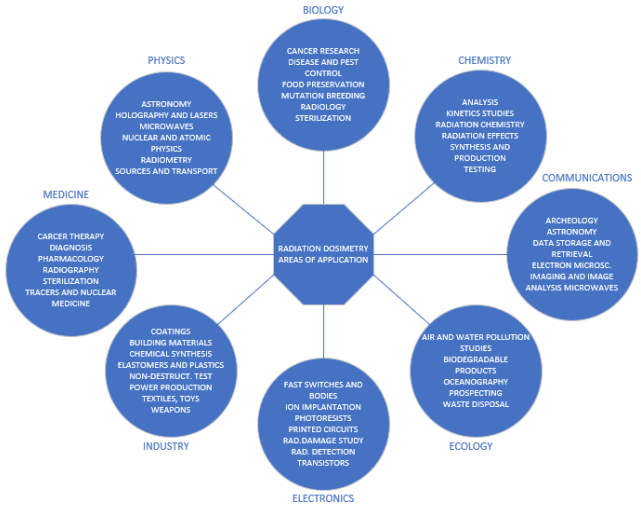

Fig. 5 *Dosimetry areas of application [11]*

The focus on quality control in producing the sterile medical devices can not be only based on QC in sterilization facility, it should be more of a system. The emphasis on quality control only in radiation processing without harmonization it with the other parts of the whole process of manufacture of a final product may not allow a final product to have been of required quality as a whole [12]. Manufacturers usually emphasize validation processes to choose the right type of sterilization and accurate dose, suitable materials of the device.

3.2. Effectiveness of sterilization

When radiation sterilization method is used to maintain sterilization process effectiveness usually dose audits are completed. The frequency of dose audits depends on many factors. In example, average bioburden level, equipment re-calibrations, maintenance of production equipment, change controls of the processes. When larger time interval is defined, proof and strong justification is required.

Bioburden

CFU / device	Method of dose determination	Max. interval dose-audit
≥ 1.5	Any	Quarterly
<1.5	Method 2 or VD max25	Quarterly
< 1.5	Method 1 or VD max15	Monthly
Any	Individual LOT release	Every individual LOT

Fig. 6 *Maintenance of radiation sterilization effectiveness based on bioburden*

ETO sterilization process effectiveness can be maintained by periodic control, justified regular and defined requalification of sterilization process, equivalence assessment. Medical devices that is sterilized by ethylene oxide sterilization method is marked very clearly. Special standards for this method are applicable because ETO is cancerogenic, mutagenic and reproductive toxic. Residuals after this sterilization can cause irritation of skin, eyes, blisters, burns and mutagenic – chromosomal defects.

There is a lot of factors when choosing the right type of sterilization for produce divice, but the comparison between most commom sterilization methods can be seen in Fig. 7.

Characteristic	Irradiation	Ethylene oxide	Steam
Efficiency	Excellent	Excellent	Excellent
Material compatibility	Majority of materials, some are decoloured, becomes brittle, are degraded	Majority of materials, not suitable for non-porous materials, liquids	Some materials, not suitable for temperature sensitive
Mechanism of action	Ionisation, damages in the DNA structure	Alcylation, damages in the DNA structure	Denaturation of proteins
Post-process control	Dose release, parametric	Biological indicators, parametric release	Biological indicators, parametric release
Quarantene	No quarantene (or 2-7 days)	2-7 days, until noEtO residuals are left	No quarantene (or 2-7 days)
Economical aspect	Very good for large and small volumes, high investment	Very good, small investment	Very good, the smallest investment

Fig. 7 *Comparison of the most frequent sterilization methods*

After sterilization medical device or product must be labeled accordingly the sterilization method used (Fig. 8)

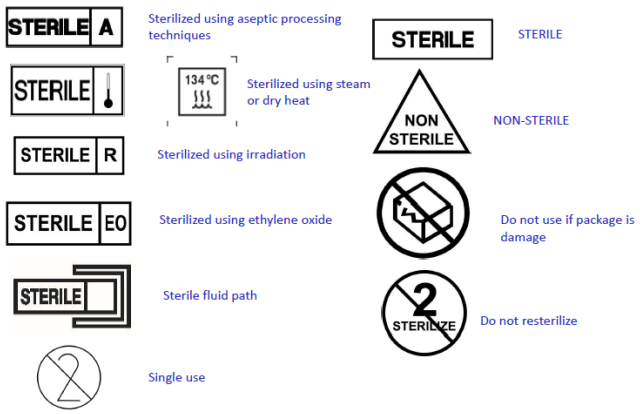

Fig. 8 *Labeling of sterile medical device*

Although, most manufacturers ships already finished product/device to sterilization facility, and it is already labelled as sterile even though it is non-sterile. Some specific restrictions and agreements are used in these situations, and some manufacturers

usually considers to have additional visual indicator on the package so the end user would sure, that the product is sterile.

4. Conclusions

Manufacturing sterile medical devices is strictly regulated by dozens of standards and guidelines instituted by various organization across the world. Various types of sterilization and irradiation methods may be used to sterilize the final product. The method may be chosen carefully according to the use of the product, raw materials that is used to manufacture it and most importantly end user. Different types of indicators could be used throughout the process to assure successful completion. Quality control of the sterilization process must be harmonized with QC in manufacturers facility to ensure the best quality products reaches the customers.

Acknowledgements

Research was funded by a grant (No. S-M-ERA.NET-20-1) (project: “Additive Manufactured Composite Smart Structures with Embedded Fibre Bragg Grating Sensors”, acronym: “AMCSS”) from the Research Council of Lithuania

4. References

1. Manmohan Singhal, MD. Habban Akhter, Devesh Kapoor, Lakshmi Kanta Kanthal, Yashu Chourasiya, Rahul Maheshwari, Anil Pethe, Rakesh K. Tekade. Advancements in sterile products and admixtures. The Future of Pharmaceutical Product Development and Research. Academic Press (2020)
2. Sam A. Hout, Sterile manufacturing. Regulations, processes, and guidelines (2021)
3. M. Gudeppu, S. Sawant, C. G. Chockalingam, & P.S. Timiri Shanmugam. Medical device regulations. Trends in Development of Medical Devices (2020)
4. Laurence W. McKeen, The Effect of Sterilization on Plastics and Elastomers (2018)
5. Moondra, Shruti. Dosage Form Design Parameters. Sterilization of Pharmaceuticals Technology, Equipment, and Validation (2018)
6. Hu, Shih-Cheng; Shiue, Angus. Validation and application of the personnel factor for the garment used in cleanrooms, Building and Environment (2016)
7. https://www.pharmamicroresources.com/2018/02/distribution-of-particles-within.html
8. https://www.pharmaguideline.com/2012/07/overview-of-iso-14644-clean-room.html
9. Fatima Hasanain, Katharina Guenther, Wayne M. Mullett and Emily Craven. Gamma Sterilization of Pharmaceuticals. A Review of the Irradiation of Excipients, Active Pharmaceutical Ingredients, and Final Drug Product Formulations. *PDA Journal of Pharmaceutical Science and Technology* March, 68 (2) 113-137 (2014).
10. Novikova Ye, Indicators of sterilization of medical products. National University of Pharmacy (2020)
11. William L. McLaughlin, Radiation measurements and quality control. , 9(1-3), 147–181 (1977)
12. V. N. Ponomarev, A. A. Molin, V. V. Kalashnikov, Ju. A. Drabkin. QC/QA system in radiation sterilization process on E-Beam irradiation plant, Department of radiation technologies of state research center (2006)