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Čiste sobe in podobna nadzorovana okolja - Kontrola biokontaminacije

Cleanrooms and associated controlled environments - Biocontamination control

Reinräume und zugehörige Reinraumbereiche - Biokontaminationskontrolle

Salles propres et environnements maîtrisés apparentés - Maîtrise de la biocontamination

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Cleanrooms and associated controlled environments - Biocontamination control

Salles propres et environnements maîtrisés apparentés - Maîtrise de la biocontamination

Reinräume und zugehörige Reinraumbereiche - Biokontaminationskontrolle

This European Standard was approved by CEN on 4 November 2019.

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EUROPEAN COMMITTEE FOR STANDARDIZATION
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CEN-CENELEC Management Centre: Rue de la Science 23, B-1040 Brussels

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European foreword

This document (EN 17141:2020) has been prepared by Technical Committee CEN/TC 243 “Cleanroom technology”, the secretariat of which is held by BSI.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by February 2021, and conflicting national standards shall be withdrawn at the latest by February 2021.

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

This document supersedes EN ISO 14698-1:2003, EN ISO 14698-2:2003 and EN ISO 14698-2:2003/AC:2006.

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

Introduction

Clean controlled environments are used to control and limit microbiological contamination where there is a risk to product quality, patient or consumer.

In this document the term “clean controlled environments” is used to cover cleanrooms, clean zones, controlled zones, clean areas and clean spaces.

This document gives guidance on best practice for establishing and demonstrating control of airborne and surface microbiological contamination in clean controlled environments. This document describes the requirements for microbiological contamination control and provides guidance on the qualification and verification of clean controlled environments.

In order to establish microbiological control, it is important to understand the risks of microbiological contamination. This is achieved by considering the sources of microbiological contamination, the associated microbiological concentrations and the likelihood of transfer and the impact on product quality, the patient or the consumer.

A formal system of microbiological control identifies, controls and monitors microbiological contamination on an ongoing basis. This is a process of continuous improvement and the principles of Plan – Do – Check – Act (PDCA) apply, as shown in Figure 1.

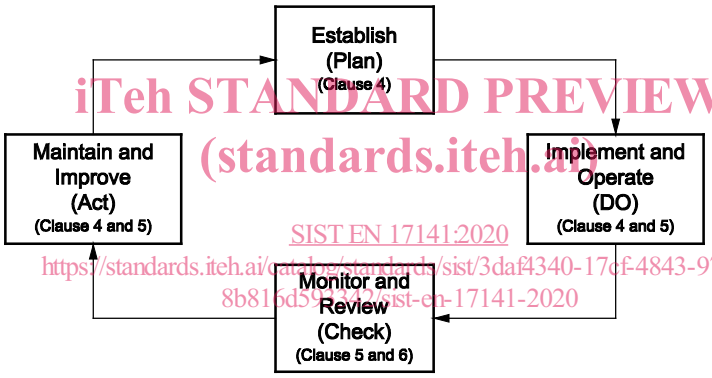

Figure 1 — Application of PDCA as the system for microbiological control

This document provides general guidance and considerations for a number of different applications. It is expected to have particular use in the Pharmaceutical, Biopharmaceutical, Medical Devices and other Life Science industries, as well as in Healthcare and Hospitals, Food, and related applications which use clean controlled environments.

In the regulated Pharmaceutical and Biopharmaceutical manufacturing sector there are already many applicable standards and regulatory guidelines. These include the EU Annex 1 GMP [31] guidance on the manufacture of Sterile Medicinal products and the FDA Aseptic Processing guidance [32]. The European and United States Pharmacopoeias also provide some guidance on certain related topics. There are numerous other documents and technical papers available from industry associations including the Parenteral Drugs Association (PDA), International Society of Pharmaceutical Engineering (ISPE) and Pharmaceutical Healthcare Sciences Society (PHSS). While there are regulations and standards on risk management of medical devices, for example EN ISO 14971 [2], there is less guidance on the microbiological control of clean controlled environments.

In the Healthcare and Hospital sector there are EU Directives, including the Tissue and Blood Directives for specialist and similar clean controlled environments. There are national standards and guidelines for specialised Operating Theatres, Isolation units, Immuno-compromised wards as part of infection

control. In addition, Hospital Pharmacy aseptic compounding units, Radiopharmacies and specialist laboratories such as Stem Cell typically refer to Life Science industry guidance documents.

In the Food and consumer related industries, while there are regulations and standards on food, beverages and cosmetics for example there is insufficient guidance regarding microbiological control in clean controlled environments.

This document includes a number of informative annexes that provide further guidance on biocontamination control in specific applications, and includes, for example:

— tables of microbiological cleanliness levels for monitoring of microbiological contamination in certain types of clean controlled environments;

— guidance in specific areas of microbiological control relating to the choice of environmental monitoring (EM) sampling methods, the management and trending of collected data and the role of alternative and real time microbiological detection systems;

— appropriate methods for establishing control, selecting appropriate alert and action levels and target levels as necessary;

— establishing a microbiological environmental monitoring plan as part of demonstrating control of the clean controlled environment.

1 Scope

This document establishes the requirements, recommendations and methodology for microbiological contamination control in clean controlled environments. It also sets out the requirements for establishing and demonstrating microbiological control in clean controlled environments.

This document is limited to viable microbiological contamination and excludes any considerations of endotoxin, prion and viral contamination.

There is specific guidance given on common applications, including Pharmaceutical and BioPharmaceutical, Medical Devices, Hospitals and Food.

2 Normative references

The following document is referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

EN ISO 14644-1:2015, *Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness by particle concentration (ISO 14644-1:2015)*

3 Terms and definitions

For the purposes of this document, biocontamination control and microbiological control are synonymous, and the following terms and definitions apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— IEC Electropedia. available at http://www.electropedia.org/

— ISO Online browsing platform: available at http://www.iso.org/obp

3.1
action level
level set by the user in the context of controlled environments, which, when exceeded, requires immediate intervention, including investigation of cause, and corrective action

3.2
alert level
level set by the user in the context of controlled environments, giving early warning of a drift from normal conditions, which, when exceeded, should result in increased attention to the process

3.3
clean controlled environment
defined zone in which microbiological contamination is controlled by specified means

3.4
cleanroom
room within which the number concentration of airborne particles is controlled and classified, and which is designed, constructed and operated in a manner to control the introduction, generation, and retention of particles inside the room

Note 1 to entry: The class of airborne particle concentration is specified.

Note 2 to entry: Levels of other cleanliness attributes such as chemical, viable or nanoscale concentrations in the air, and also surface cleanliness in terms of particle, nanoscale, chemical and viable concentrations may also be specified and controlled.

Note 3 to entry: Other relevant physical parameters may also be controlled as required, e.g. temperature, humidity, pressure, vibration and electrostatic.

[SOURCE: EN ISO 14644-1:2015, 3.1.1, [1]]

3.5
clean zone
defined space within which the number concentration of airborne particles is controlled and classified, and which is constructed and operated in a manner to control the introduction, generation, and retention of contaminants inside the space

Note 1 to entry: The class of airborne particle concentration is specified.

Note 2 to entry: Levels of other cleanliness attributes such as chemical, viable or nanoscale concentrations in the air, and also surface cleanliness in terms of particle, nanoscale, chemical and viable concentrations may also be specified and controlled.

Note 3 to entry: A clean zone(s) may be a defined space within a cleanroom or may be achieved by a separative device. Such a device may be located inside or outside a cleanroom.

Note 4 to entry: Other relevant physical parameters may also be controlled as required, e.g. temperature, humidity, pressure, vibration and electrostatic.

[SOURCE: EN ISO 14644-1:2015, 3.1.2, [1]]

3.6
colony forming unit
formation of a single macroscopic colony after the introduction of one or more microorganisms to microbiological growth media

Note 1 to entry: One colony forming unit is expressed as 1 cfu.

3.7
critical control point
specific point, procedure, or step in the process at which control can be exercised to reduce, eliminate, or prevent the possibility of microbiological contamination

3.8
critical zone
designated space within the clean controlled environment used to control microbiological contamination

3.9
culturable
having the ability to grow and form colony forming units (cfu), using microbiological culturing techniques

3.10
environmental monitoring
EM
measurement of specified parameters at periodic intervals within a clean controlled environment

3.11
microorganism
entity of microscopic size encompassing bacteria fungi protozoa and viruses

Note 1 to entry: Microbe is synonymous with microorganism.

Note 2 to entry: The use of the term microorganism in this standard includes bacteria, yeast and moulds only.

[SOURCE: ISO 17665-1:2006, 3.25, [50]]

3.12
microorganism of interest
microbiological contamination that has been identified as harmful to the product or the process, or the intended recipient of the product within the clean controlled environment

Note 1 to entry: This includes commonly used terms such as objectionable species, microorganism of concern or Pathogenic microorganisms or specified microorganisms.

3.13
risk assessment
actions to determine the likelihood and consequences of microbiological contamination within the clean controlled environment

3.14
sterile
free from viable microorganisms

[SOURCE: ISO/TS 11139:2018, [51]]

3.15
sterilisation
validated process used to render a product free from viable microorganisms

[SOURCE: ISO/TS 11139:2018, [51]]

3.16
target level
defined level set by the user as a goal for routine operations, for the user's own purpose

3.17
validation
confirmation, through the provision of objective evidence that the requirements for a specific intended use or application have been fulfilled

Note 1 to entry: The objective evidence needed for a validation is the result of a test or other form of determination such as performing alternative calculations or reviewing documents.

Note 2 to entry: The word "validated" is used to designate the corresponding status.

Note 3 to entry: The use conditions for validation can be real or simulated.

[SOURCE: EN ISO 9000:2015]

3.18
verification
confirmation, through the provision of objective evidence, that specified requirements have been fulfilled

Note 1 to entry: The objective evidence needed for a verification can be the result of an inspection or of other forms of determination such as performing alternative calculations or reviewing documents.

Note 2 to entry: The activities carried out for verification are sometimes called a qualification process.

Note 3 to entry: The word "verified" is used to designate the corresponding status.

[SOURCE: ISO 9000:2015]

3.19
viable
microorganism, alive and either culturable or non culturable

3.20
viable particle
particle that contains one or more living microorganism

4 Establishment of microbiological control

4.1 General

When the clean controlled environment is classed as a cleanroom or clean zone the requirements of EN ISO 14644-1, shall be complied with.

4.2 Establishing a formal system for microbiological control

A system to maintain appropriate microbiological contamination control shall be established, implemented and maintained. The system shall identify, control and monitor factors that can affect microbiological contamination of the product. The outputs of the system shall be documented

There are a number of accepted microbiological contamination control systems that utilise a quality risk management approach [2], [3], [5], [6], [8] [9]; the selected system shall be appropriate and verified.

4.3 Microbiological contamination control system quality attributes

The microbiological contamination control system shall consider the following steps:

a) identification of all potential microbiological contamination sources and routes of contamination in the clean controlled environment, deemed microorganisms of interest;

b) assessment of the risk from these sources and routes and, where appropriate, introduce or improve microbiological contamination control methods to reduce the identified risks;

c) establishment of a monitoring schedule, with valid sampling methods, to monitor the microbiological contamination source, or their control methods or both;

d) establishment of alert and action levels, and where appropriate target levels, with measures to be taken when required, if these levels are exceeded;

e) verification on a continuing basis, that the microbiological contamination control system is effective and meeting agreed performance parameters by reviewing product contamination rates, environmental monitoring results, risk assessment methods, control methods and monitoring limits and, where appropriate, modify them accordingly;

f) establishment and maintenance of appropriate documentation;

g) education and training of all staff involved with the clean controlled environment.

4.4 Identification of all potential sources and routes of microbiological contamination

4.4.1 General

Before the risk assessment process can start the nature of the process should be investigated and understood.

All potential microbiological contaminants, and their routes of transfer, that pose a risk to the product, patient or consumer shall be identified.

Microbiological contamination can come from people and what they wear, materials, equipment, services and processes, the physical condition of the facility and surrounding environment as well as the supply air, airflow patterns and movement within the clean controlled environment, and ongoing cleaning. When there is a risk of product or process contamination from particular types of microorganisms these can be considered as microorganisms of interest.

Microorganisms of interest shall be identified during the risk assessment process.

The following factors should be considered as part of the risk assessment:

a) clean controlled environment application, (e.g. pharmaceutical, medical device, food, cosmetics);

b) microbiological species, (e.g. survival possibility, or associated toxins);

c) potential for causing microbiological contamination of the product and/or harm to the intended recipient, (e.g. spoilage of product prior to end of shelf life in food);

d) product form (e.g. does the product contain preservatives, or any potential growth substrates that may prevent growth);

e) intended product target population (e.g. patient, infant, immuno-compromised recipient);

The presence of moulds and other microbiological contamination, including microorganisms of interest, can be indicators of poor cleaning or poor design and increase the risk of product and/or process contamination.

Arising from a risk assessment, action and alert, and if appropriate target levels for routine monitoring can be set for total microbiological concentrations without reference to the microorganisms of interest or by consideration of both.

When the initial qualification of a new non-operating premises or where the activity is not yet representative of normal operation, microbiological contamination may not be sufficiently representative. It may therefore be necessary to re-evaluate the risk in normal operation.

4.4.2 Sources of microbiological contamination

4.4.2.1 General

Sources of microbiological contamination can be prime and derived or associated.

4.4.2.2 Prime sources

The following are examples of prime sources:

— People - A major source of contamination;

— Supply Air - Air supplied into clean controlled environments. (re-circulated or fresh make up);

— Product Materials - Product in solid or liquid form, containers and packaging;

— Utilities - Compressed air, nitrogen, propane, oxygen, WFI;

— Machines - Processing and packaging equipment.

4.4.2.3 Derived or associated sources

The following are examples of derived or associated sources:

— Air Within - Air within clean controlled environments;

— Contact Parts- Product contacting parts such as pipework and closure hoppers;

— Surfaces - Clean controlled environment floors, walls, workstation surfaces, barrier gauntlets, trolleys, buckets, balances, disinfectant containers, monitoring devices;

— Adjacent Areas - Change rooms, corridors, pass through transfer hatches.

4.4.3 Routes of transfer of microbiological contamination

There are 3 routes of transfer of microbiological contamination to the product or critical zone in a clean controlled environment:

— airborne deposition;

— surface contact;

— liquid.

NOTE The transfer of potential sources of microbiological contamination via the liquid route is not part of the scope of this document.