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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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Salles propres et environnements maîtrisés apparentés - Maîtrise de la biocontamination

Reinräume und zugehörige Reinraumbereiche - Biokontaminationskontrolle

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EUROPEAN COMMITTEE FOR STANDARDIZATION
COMITÉ EUROPÉEN DE NORMALISATION
EUROPÄISCHES KOMITEE FÜR NORMUNG

CEN-CENELEC Management Centre: Rue de la Science 23, B-1040 Brussels

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European foreword

This document (prEN 17141:2018) has been prepared by Technical Committee CEN/TC 243 “Cleanroom technology”, the secretariat of which is held by BSI.

This document is currently submitted to the second CEN Enquiry.

The first Enquiry was approved in September 2017 but with such a large number of comments and recommendations relating to both the content and structure of the standard it was decided to prepare a second publication in response.

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

This standard gives guidance on best practice for establishing and demonstrating control of airborne and surface microbiological contamination in clean controlled environments. This standard 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 necessary 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.

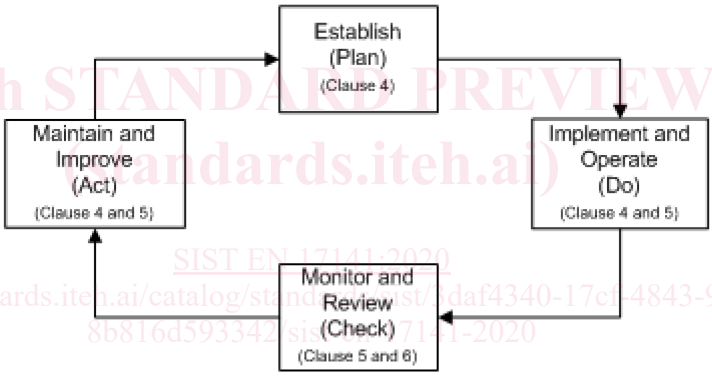

Figure 1 — Application of PDCA as the system for microbiological control

This standard 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 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 PIC/S Annex 1 GMP guidance documents on the manufacture Sterile Medicinal products, the FDA Aseptic Processing guidance document and the WHO GMP guidance on good manufacturing practice. The European and United States Pharmacopoeias also provide some guidance on certain related topics. And there are numerous other documents and technical papers available from industry associations including the PDA, ISPE and PHSS. While there are regulations and standards on risk management of medical devices, for example EN ISO 14971, 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 Labs 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 Labs 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.

Informative annexes give tables of microbiological cleanliness levels for monitoring of microbiological contamination in certain types of clean controlled environments. Other informative annexes offer additional 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, as well as guidance on appropriate methods for establishing control, selecting appropriate alert and action levels and 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 Pharma/BioPharma, 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, *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
aseptic
conditions and procedures used to exclude the introduction of microbial microbiological contamination

[SOURCE: ISO 14161:2009]

3.2
clean controlled environment
defined zone in which microbiological contamination is controlled by specified means

3.3
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: ISO 14644-1:2015, 3.1.1]

3.4
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: ISO 14644-1:2015, 3.1.2]

3.5
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.

3.6
controlled zone
designated space in which the concentration of at least one contamination category (particles, chemical, biocontamination) in air and/or on surfaces is controlled and specified and which is constructed and used in a manner to minimize the introduction and impact of contamination

Note 1 to entry: Levels of cleanliness attributes such as viable concentrations in the air or cleanliness in terms of particle and viable concentrations on surfaces may be specified by class(es).

Note 2 to entry: Other relevant parameters may also be controlled as necessary, e.g. temperature, humidity and pressure, vibration and electrostatic.

Note 3 to entry: A controlled zone can 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: The term biocontamination is synonymous with microbiological contamination.

[SOURCE: ISO 14644-15:2017, 3.9.]

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, using microbiological culturing techniques

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

Note 1 to entry: Environmental monitoring can include measurements such as particle counts and microbiological sampling methods such as airborne, settle plates, swabs, etc.

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

Note 1 to entry: Microbes is synonymous with microorganism.

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

[SOURCE: ISO 17665-1:2006 3.25]

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 14160:2011]

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

[SOURCE: ISO 14937:2009]

3.16
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: ISO 9000:2015]

3.17
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]

3.18
viable
microorganism, alive and either culturable or non culturable

3.19
viable particle
particle that contains one or more living microorganisms

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 [4], [5], [7], [8], [10]; 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 appropriate target, alert and action 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. These shall be categorised as microorganisms of interest.

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.

Microorganisms of interest shall be identified during the risk assessment process. The following factors should be considered:

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);

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

NOTE 1 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.

NOTE 2 Action and alert levels, arising from the risk assessment and routine monitoring can be set by total microbiological concentrations without reference to the microorganisms of interest or by consideration of both of these.