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Cleanrooms and associated controlled environments — Biocontamination control —

Part 1: General principles and methods

Salles propres et environnements maîtrisés apparentés — Maîtrise de la biocontamination —

Partie 1: Principes généraux et méthodes

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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

ISO 14698-1 was prepared by Technical Committee ISO/TC 209, *Cleanrooms and associated controlled environments*.

ISO 14698 consists of the following parts, under the general title *Cleanrooms and associated controlled environments — Biocontamination control*:

— *Part 1: General principles and methods*

— *Part 2: Evaluation and interpretation of biocontamination data*

Introduction

The principles described here are intended to promote appropriate hygienic practices. This part of ISO 14698 is one of a number of standards considering factors important for the creation of clean, controlled environments.

Hygiene has become increasingly important in many areas of modern society. In such areas, hygiene or biocontamination control methods are, or will be, used to create safe and stable products. International trade in hygiene-sensitive products has greatly increased. At the same time, the use of antimicrobial agents has been reduced or forbidden, creating a need for increased biocontamination control.

This part of ISO 14698 is the first general International Standard for biocontamination control. However, many factors besides cleanliness must be considered in the design, specification, operation and control of cleanrooms and associated controlled environments.

In some circumstances, relevant regulatory agencies could impose supplementary policies or restrictions. In such situations, appropriate adaptations of the standard testing procedures might be required.

Cleanrooms and associated controlled environments — Biocontamination control —

Part 1: General principles and methods

1 Scope

This part of ISO 14698 establishes the principles and basic methodology of a formal system of biocontamination control (Formal System) for assessing and controlling biocontamination when cleanroom technology is applied for that purpose. This part of ISO 14698 specifies the methods required for monitoring risk zones in a consistent way and for applying control measures appropriate to the degree of risk involved. In zones where risk is low, it can be used as a source of information.

Application-specific requirements are not given. Neither are fire and safety issues addressed; for these, see regulatory requirements and other national or local documentation.

2 Normative references

The following referenced documents are indispensable for the application 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.

ISO 14644-4:2001, *Cleanrooms and associated controlled environments — Part 4: Design, construction and start-up*

ISO 14698-2:2003, *Cleanrooms and associated controlled environments — Biocontamination control — Part 2: Evaluation and interpretation of biocontamination data*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

3.1 General

3.1.1
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

3.1.2
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

3.1.3
bioaerosol
dispersed biological agents in a gaseous environment

3.1.4
biocontamination
contamination of materials, devices, individuals, surfaces, liquids, gases or air with viable particles

3.1.5
cleanroom
room in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room, and in which other relevant parameters e.g. temperature, humidity, and pressure, are controlled as necessary

[ISO 14644-1:1999, 2.1.1][1]

3.1.6
contact device
specially designed appliance holding an appropriate, sterile, culture medium with an accessible surface used for surface sampling

3.1.7
contact plate
contact device where the container is a rigid dish

3.1.8
control point
point in a controlled environment at which control is applied and a hazard can be prevented, eliminated or reduced to acceptable levels

3.1.9
controlled environment
defined zone in which sources of contamination are controlled by specified means

3.1.10
corrective action
action to be taken when the results of monitoring indicate that alert or action levels are exceeded

3.1.11
Formal System
system of biocontamination control with established and documented procedures

3.1.12
hazard
potential source of harm

[ISO/IEC Guide 51:1999, 3.5][2]

3.1.13
impact sampler
device designed to sample particles in the air, or other gas, through a collision with a solid surface

3.1.14
impingement sampler
device designed to sample particles in the air, or other gas, through a collision with a liquid surface and the subsequent entering into the liquid

3.1.15
qualification
process of demonstrating whether an entity — activity or process, product, organization, or any combination thereof — is capable of fulfilling specified requirements

3.1.16
risk
combination of the probability of occurrence of harm and the severity of that harm

[ISO/IEC Guide 51:1999, 3.2][2]

3.1.17
risk zone
defined and delimited space where individuals, products or materials (or any combination of these) are particularly vulnerable to contamination

3.1.18
settle plate
suitable container (e.g. a Petri dish) of appropriate size, containing an appropriate, sterile, culture medium, which is left open for a defined period to collect viable particles depositing from the air

3.1.19
swab
sterile collection device, non-toxic and non-inhibitory to the growth of the microorganisms being sampled, consisting of a specific matrix of suitable size, mounted on an applicator

3.1.20
target level
defined level set by the user as a goal for routine operations, for the user's own purpose

3.1.21
validation
confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

[ISO 9000:2000, 3.8.5][3]

3.1.22
verification
confirmation, through the provision of objective evidence, that specified requirements have been fulfilled

[ISO 9000:2000, 3.8.4][3]

NOTE Monitoring and auditing methods, procedures and tests, including random sampling and analysis, can be used in the verification of the Formal System.

3.1.23
viable particle
particle that consists of, or supports, one or more live microorganisms

3.1.24
viable unit
VU
one or more viable particles which are enumerated as a single unit

NOTE When viable units are enumerated as colonies on agar media, it is common usage to name them colony forming units (CFU). One CFU might consist of one or more VU.

3.2 Occupancy states

3.2.1
as-built
condition where the installation is complete with all services connected and functioning, but with no production equipment, materials or personnel present

[ISO 14644-1:1999, 2.4.1][1]

3.2.2
at-rest
condition where the installation is complete with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present

[ISO 14644-1:1999, 2.4.2][1]

3.2.3
operational
condition where the installation is functioning in the specified manner, with the specified number of personnel present and working in the manner agreed upon

[ISO 14644-1:1999, 2.4.3][1]

4 Principles of biocontamination control

4.1 A formal system of biocontamination control (Formal System) shall be established, implemented and maintained within cleanrooms and associated environments. The Formal System will assess and control factors that can affect the microbiological quality of the process and product.

There are a number of accepted methods for achieving this goal by risk assessment[4], [5]. The hazard analysis critical control point (HACCP) system[6], [7], [8], [9] is commonly used. Fault tree analysis (FTA)[10], or the failure mode and effect analysis (FMEA)[11], or any other validated equivalent system can be used.

In many such methods, any type of hazard can be considered. Within this part of ISO 14698, only microbiological hazards are addressed.

4.2 To assess and control the microbiological hazards, any selected system shall address the following principles:

a) identification of potential hazard(s) to the process or product, assessment of the likelihood of occurrence of these hazard(s), and identification of measures for their prevention or control;

b) designation of risk zones and, in each zone, determination of the points, procedures, operational steps and environmental conditions that can be controlled to eliminate the hazard(s) or minimize the likelihood of their occurrence;

c) establishment of limits to ensure control;

d) establishment of a monitoring and observation schedule;

e) establishment of corrective actions to be taken when monitoring results indicate that a particular point, procedure, operational step or environmental condition is not under control;

f) establishment of procedures, which may include supplementary tests and procedures, to verify that the chosen Formal System is working effectively;

g) establishment of training procedures;

h) establishment and maintenance of appropriate documentation.

5 Establishing the Formal System

5.1 General requirements

It is the responsibility of the user to develop, initiate, implement and document a Formal System for biocontamination control that allows detection of adverse conditions in a timely fashion. It is imperative that such a programme be tailored to the field of application, to the specific facility and to specified conditions, and that this system be an integral part of a quality management system. The quality management system shall include an appropriate training programme for the selected Formal System.

In addition, it is essential that a monitoring programme (see 5.3) be designed and implemented in a manner that minimizes the possibility of the sampling activities themselves contributing to the contamination of the product or risk zone or both.

Risk zones shall be classified according to relevant guidelines, regulations (where these exist) and the chosen Formal System. Risk zones may also be classified according to the level of aerial and surface biocontamination, for example, low, medium, high or very high risk.

NOTE The first two parts of a Formal System, as given in 4.2 a) and b), are not discussed in detail in this part of ISO 14698, but information on how to identify, assess and control hazards is given in other sources. See, for example, [12].

5.2 Alert, action and target levels

The user of a cleanroom or controlled environment shall set microbiological alert and action levels. These levels shall be appropriate to the field of application, to the classification of the risk zones and to what is achievable using current technology. Microbiological target levels may be used as an alternative to microbiological alert and action levels in some specific fields of application.

During initial start-up and at intervals established according to the Formal System, data on biocontamination levels should be reviewed to establish or confirm a baseline for the determination of alert and action levels. Alert and action levels may be related to the target levels in any specific applications where these are set. Alert and action levels should be reviewed and adjusted as appropriate.

5.3 Monitoring of biocontamination

5.3.1 General

Detection and monitoring of biocontamination in risk zones shall be carried out by sampling and enumerating viable units with appropriate methods in accordance with a sampling plan.

Examples of sources of biocontamination that can constitute a hazard are air, surfaces, textiles and liquids (see Annexes A, C, D and F).

Microbiological sampling may be useful for providing baseline data as new installations are constructed and commissioned, including, as relevant, in the as-built state. Monitoring in risk zones shall be performed when the installation is in the as-built and at-rest states. Monitoring shall also be performed routinely in the operational state according to the selected Formal System.

5.3.2 Sampling

5.3.2.1 General

The appropriate sampling method and related procedures shall be selected and performed to reflect the complexity and variety of situations. Sampling shall be carried out using a device and method selected in accordance with the written procedure and in accordance with the instructions provided by the device manufacturer.

5.3.2.2 Sampling device

A sampling device shall be selected according to the area being monitored. The selection for a particular application shall take into consideration the following factors:

a) type of viable particles for which to sample;

b) sensitivity of the viable particles to the sampling procedure;

c) expected concentration of the viable particles;

d) indigenous microbial flora;

e) accessibility of the risk zones;

f) ability to detect low levels of biocontamination;

g) ambient conditions in the risk zone being sampled;

h) time and duration of sampling;

i) sampling method, material and properties of the sampling medium;

j) effect of the sampling device on the process or environment to be monitored;

k) collection accuracy and efficiency;

l) incubation and viable particle detection and evaluation method;

m) type of information to be obtained (e.g. qualitative or quantitative aspects);

n) efficiency of extraction/rinse fluids, where appropriate.

5.3.2.3 Sampling plan

A sampling plan shall be developed through the selected Formal System and shall be documented. A documented sampling plan is essential for accurately assessing and interpreting biocontamination data.

Sampling shall be carried out when the area is in the operational condition and during periods of greatest stress in the system, for example, before the end of a shift or when the greatest amount of activity is taking place. Sampling in the at-rest condition may also provide useful information about the facility design and performance.

The sampling plan shall comprise the following:

a) initial sampling plan to provide a reference point or baseline within the framework of the chosen Formal System;

b) routine sampling plan resulting from the implementation of the chosen Formal System.

5.3.2.4 Design of the sampling plan

The sampling plan shall take into account the cleanliness level of the risk zone and the degree of biocontamination control required for the activity being conducted, to protect individuals, the environment, the process and the product. The following are examples of elements to be considered:

a) choice of the sampling location, taking account of the location and function of the risk zone;