

Institute of Environmental Sciences and Technology

IENT-RP-CC018.5

Contamination Control Division
Recommended Practice 018.5

Cleanroom Cleaning and Sanitization: Operating and Monitoring Procedures



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CLEANROOM CLEANING AND SANITIZATION: Operating and Monitoring Procedures IEST-RP-CC018.5

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1 SCOPE AND LIMITATIONS

1.1 Scope

This Recommended Practice (RP) provides guidance for maintaining a cleanroom at the level for which it was intended. This document is presented as a guide for establishing appropriate cleaning and sanitization procedures essential for the overall contamination control program of the cleanroom. In addition, test procedures are provided for use in establishing the frequency of cleaning and sanitization and monitoring the effectiveness.

The test methods also are designed to help determine appropriate levels of surface cleanliness for specific cleanrooms.

1.2 Limitations

This RP does not specify acceptance limits, but does provide standard terminology for specifying desired limits.

NOTE: References to “cleanroom” in this document are to be construed, where appropriate, as including clean zones and clean-air devices.

2 REFERENCES

The cited editions of the following documents are incorporated into this RP to the extent specified herein. Users are encouraged to investigate the possibility of applying the most recent editions of the references.

2.1 American Society for Testing and Materials (ASTM)

ASTM F24-09: Standard Method for Measuring and Counting Particulate Contamination on Surfaces

2.2 Institute of Environmental Sciences and Technology (IEST)

IEST-RP-CC003.4: Garment System Considerations in Cleanrooms and Other Controlled Environments

IEST-RP-CC004.3: Evaluating Wiping Materials Used in Cleanrooms and Other Controlled Environments

IEST-RP-CC005.4: Gloves and Finger Cots Used in Cleanrooms and Other Controlled Environments

IEST-RP-CC007.3: Testing ULPA Filters

IEST -RP-CC022.2: Electrostatic Charge in Cleanrooms and Other Controlled Environments

IEST-RP-CC044.1: Vacuum Cleaners and Systems for Cleanrooms and Controlled Environment

2.3 International Organization for Standardization (ISO)

ISO 14644-1:2015 Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness

2.4 United States Pharmacopeia (USP)

USP-NF: The United States Pharmacopeia and National Formulary

2.5 Sources and Addresses

ASTM

American Society for Testing and Materials

100 Barr Harbor Drive

West Conshohocken, PA 19428-2959 USA

Phone: 610-832-9585

Fax: 610-832-9555

Web: www.astm.org

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ISO

In the US, documents may be ordered from:

INSTITUTE OF ENVIRONMENTAL SCIENCES AND TECHNOLOGY

Outside the US: Documents available from representative ISO member body organization

USP

United States Pharmacopeia

12601 Twinbrook Parkway

Rockville, MD 20852-1790 USA

Phone: 301-881-0666

Fax: 301-816-8148

Web: www.usp.org

3 TERMS AND DEFINITIONS

adhesion

The force exerted across a surface of contact between liquids and solids, or solids and solids, that resists their separation.

classes of air cleanliness

The airborne particle concentration levels defined by ISO 14644-1.

cleaning agent

Any liquid that has the ability to aid in the removal of surface contamination, is compatible with the product and process, and does not contribute substantially to the contamination of the cleanroom.

cleanroom

A room in which the air filtration, air distribution, utilities, materials of construction, equipment, and operating procedures are specified and regulated to control airborne particle concentrations to meet appropriate airborne particulate cleanliness classifications, as defined by ISO 14644-1.

clean zone

A defined space in which the concentration of airborne particles is controlled to specified limits.

contamination

The result of the addition of contaminants to a material or to any surface within a clean zone.

disinfectant

A chemical or physical agent that destroys or removes vegetative forms of harmful microorganisms when applied to a surface. (USP <1972>).

filter

A device used to remove particulate matter or impurities from a fluid (gas or liquid) flowing through it.

filter, high-efficiency particulate air (HEPA)

An extended-medium, dry-type filter in a rigid frame, having a minimum particle-collection efficiency of 99.97% (i.e., a maximum particle penetration of 0.03%) for 0.3- μm particles specified aerosol.

filter, ultralow-penetration air (ULPA)

An extended-medium, dry-type filter in a rigid frame, having a minimum particle-collection efficiency of 99.999% (that is, a maximum particle penetration of 0.001%) for particles in the size range of 0.1 to 0.2 μm , when tested in accordance with the methods of IEST-RP-CC007.

housekeeping, cleanroom

Maintenance or cleaning performed to preserve the specified cleanliness of a cleanroom.

particle

An object that is solid, liquid, or both, usually between 1 nm and 1 mm in size.

particle burden

The number of particles in the relevant size range per unit area of surface.

primary surface

A surface that is in direct contact with the product.

residue

Any substance remaining on a surface after the surface has been cleaned.

sanitizer

A chemical agent that reduces the number of vegetative bacteria, some enveloped viruses, and some fungi on hard non-porous surfaces by 99.9% (3-logs).

secondary surface

A surface that is not in contact with the product, but which indirectly affects the product.

sporicidal agent

A chemical agent that destroys all vegetative bacteria, enveloped, non-enveloped viruses, fungi, and bacterial endospores on hard non-porous surfaces.

surface contaminant

Any unwanted substance present in or on a surface.

viable particle

A particle capable of reproduction; a living organism.

4 BACKGROUND

4.1 History

The methods and techniques presented in this RP originated from the initial meeting for this RP and industry standards at that time. Some of the methods were based on studies performed by universities and aerospace, semiconductor, and pharmaceutical companies. Round-robin testing (industry testing of the methods by all classes and types of cleanrooms) was done for the initial publication of the RP.

Previous revisions added one floor and one wall cleaning technique. The proposal to add these techniques was based on particle removal efficiency studies published by the University of Arizona in Tucson and microbial removal efficiency studies published by the Research Triangle Institute. For this revision, an additional wall method is included. The committee had direct oversight on the 25 companies that participated in the 6-month comparison testing of both wall and floor techniques.

4.2 Particles on surfaces: adhesion and removal

Mechanisms by which particles are held to surfaces in a cleanroom include London-van der Waals forces (the dominant mechanism when surfaces are not wetted), electrostatic forces (which usually are small if the facility has been properly shielded), and capillary adhesion. Removal of particles is aided by the use of a liquid because such usage decreases the London-van der Waals forces by several orders of magnitude, dissipates electrostatic forces, and, if a surfactant is present in the liquid, decreases capillary adhesion through a lowering of surface tension.

Ionic surfactants alter surface electrical potentials and thus also can reduce electrical forces. Liquids also permit better coupling of the mechanical energy used during cleaning, as well as provide an opportunity for the removal of soluble contaminants through dissolution.

Individual submicrometer particles are difficult to remove, and even an optimum cleaning procedure may not completely eliminate submicrometer particles from cleanroom surfaces (see Bowling, Appendix B). It is likely that only those particles larger than 5 µm may be significantly affected by the cleaning procedures presented in this RP.

See Appendix A for a detailed discussion of particle adhesion and removal.

4.3 Validation of cleaning

If cleaning is being undertaken by or for a manufacturing process, where the control of viable organisms is critical (e.g. pharmaceutical, biologic, or medical devices manufacturing), the cleaning may be under the control of a regulatory agency such as the United States Food and Drug Administration (FDA), in which case the validation of cleaning is essential.

The formal FDA definition of such validation in *Guideline on General Principles of Process Validation* can be summarized as:

“Establishing documented evidence which provides a high degree of assurance that a specific [cleaning] process will consistently produce a product [result] meeting its predetermined specifications and quality attributes.”

Validation, usually undertaken as a project prior to full-scale operation, starts with the creation of a Validation Master Plan. Most often, the plan contains three sections: strategy, protocols, and evaluation. “Strategy,” or the design phase, sets out the objectives and specifies the results to be achieved. Results are specified as permitted residual limits. “Protocols” covers the implementation stage and specifies how the goals will be achieved. “Evaluation” describes the means and methods, either visual or sampling and analytical tests, that will be used to analyze the results of the process.

Sampling techniques should be able to collect contamination, the residues, in a form that is detectable by the analytical methods of choice. That choice will depend on the sampling site, the nature and properties of the residues, and the type of facility and its equipment.

4.3.1 Cleaning

Cleaning is the removal of visible and invisible particulates and fibers on surfaces. Depending on the size of the particle, this is done by vacuuming and wet cleaning. Cleaning efficiency can be enhanced by the use of proper techniques, tools, and solutions.

4.3.2 Sanitization

There are three key steps that are key to validation of the sanitizer, disinfectant, and sporicide used in cleanroom operations:

- 1) In-Situ or worst-case testing
- 2) In-Vitro testing
- 3) Routine environmental monitoring and data trending

The in-situ testing is typically conducted after worst case events in cleanrooms such as shut downs, construction events, power failures, or adverse weather events. Generally, multiple cleanings are required after adverse events. The current industry standard is three cleanings. These three cleanings are generally two cleans with a sanitizer or disinfectant solution, and a final clean with a sporicidal agent. The objective is to gather environmental monitoring data after each phase of a triple cleaning event or after the cleaning and disinfection steps are taken to bring the cleanroom back online. There is initial environmental data gathering while the site is in a worst-case state of control and prior to the initial site

cleaning. The in-situ testing shows regulators that under worst case conditions the cleaning and sanitization program is able to keep the cleanroom in a state of control.

It is fairly common knowledge in the pharmaceutical, biotechnology, compounding industry (503B), and medical device industries that regulatory authorities expect regulated facilities to demonstrate that the biocides used in controlled environments are effective against environmental isolates on surfaces representative of the area in which they are used. Disinfectant effectiveness studies are not routine and require an extensive amount of planning whether they are performed internally or by a contract lab.

When a cleanroom site selects a new disinfectant or sporicide it may take six to twelve months to conduct the coupon testing as the site facility environmental monitoring data is analyzed over time to select the isolates for testing. PDA Technical Report #70 does indicate that a new cleanroom facility may conduct their coupon studies with the ATCC strains listed in USP <1072>, however, this will add additional cost to the overall disinfectant testing as the facility isolates will need to be tested once the site performs a gap analysis determining which specific isolates need to be tested.

In vitro testing to demonstrate effectiveness of disinfectants and sporicides, particularly those involving surface challenge, is inherently difficult to perform and presents numerous challenges. There are many factors that are critical to the study outcome, and if not carefully controlled, will lead to failures. Numerous materials, extensive preparation and significant technical resources are necessary to prepare and properly execute such a study. Failing or unexpected results compound a process that is already complex, time-consuming and expensive. The activity of a disinfectant can vary considerably from method to method even with the same product. Therefore, it is crucial that the method chosen be used throughout the disinfectant qualification study. Consistency when performing the study is critical. Once the appropriate method has been chosen, there are several parameters that must be closely controlled for consistent results. Key criteria to consider are inoculum level, neutralization, cleanroom surfaces, cleanroom environmental isolates, soil loads, water quality, and hold time studies. Risk assessments are commonly used in selecting surfaces for the coupon testing. After the initial disinfectant coupon study is completed the environmental monitoring data is checked on a yearly basis for new organisms and hard-to-kill isolates that may be included in a new coupon study. Additionally, every five to seven years all of the previous coupon testing data is evaluated to make sure there were no issues with controls, neutralization, log reduction, or study design. If there were inconsistencies in past coupon testing then repeat testing may be executed.

The final step to the disinfectant validation process is to routinely assess the cleaning and disinfection program through the environmental monitoring program and reviewing the frequencies of excursions in the cleanroom operation.

5 PROCEDURES

5.1 Equipment and supplies

All tools, equipment, and supplies used for maintaining the cleanliness of the cleanroom should be selected carefully for the intended cleanroom. Equipment should be constructed of non-shedding materials that can be easily maintained in a clean condition. Such materials may include reinforced plastic or fiberglass, powder-coated steel, anodized or hard-coated aluminum, stainless-steel, or other approved materials. Equipment utilizing casters should have polyurethane or other non-marring wheel surfaces. If sterilization or disinfection is required then, equipment and tools should be constructed of stainless-steel or other resilient materials.

The following sections list recommended supplies and equipment for use in housekeeping. It should be noted that this list is not all-inclusive. The responsible person should select equipment and supplies compatible with the cleanroom, cleanroom surfaces, the product, and related processes.

5.1.1 Vacuum cleaning system

A central plant vacuum (wet or dry) with attachments, or a portable vacuum cleaner with HEPA/ULPA-filtered exhaust and accessories.