Environmental Control Programs: What They Are and What They Should Include

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What is an Environmental Control Program?

An Environmental Control Program (ECP) is a comprehensive program that includes a written plan that outlines the steps in developing, establishing, implementing, and monitoring the environmental controls necessary to ensure that products are consistent, reproducible, and reliable. The ECP includes the following elements: facility design, construction, and operation, utilities, cleaning, raw materials and components, personnel, waste flow, preservative systems, and environmental monitoring. Environmental monitoring is merely one tool that is used to measure the program's success. The ECP also includes the procedures and documentation generated in support of the program.

An ECP plan can be developed in newly established companies prior to the transfer of the first product from development into production and Quality Control (QC). The plan, in this case, will serve as a "roadmap" for the identification and creation of the procedures, training, records, and supporting activities required to establish the ECP.

For existing companies, an ECP plan can be developed as an evaluation tool. The plan, in this case, can serve as an assessment for the adequacy of the procedures, training, and record-keeping to support a balanced ECP. A balanced program requires facility and utility design, raw material selection, cleaning procedures, personnel/material flows, preservative systems, and environmental monitoring procedures that result in a minimal risk to product and patient safety that is consistent with product and regulatory requirements.

Objectives of the Environmental Control Program

The objective of an ECP is to integrate the elements of the ECP into a balanced environment that will ensure the performance and reliability of the product consistent with regulatory requirements.

What are the key steps in developing an ECP?

❶ Define the objectives and scope of the ECP.
❷ Assign preliminary responsibilities.
❸ Prepare a plan to identify and evaluate each environment, capture responsibilities, and make assign-

ments. Refer to the sample ECP provided. Refer to the list of recommended SOPs to support the plan.

❹ Obtain senior management approval to fund and support the EPC.

❺ Execute the plan.

❻ Verify completion of the assignments, and monitor completion to ensure effectiveness. Refer to the example audit checklist located on page 16 of this article.

Elements of the Environmental Control Program

To further understand the elements that comprise the ECP, it is important to define and describe each element, and the role it plays in balancing the environment.

Implementation of the Environmental Monitoring (EM) Program requires that the following preliminary requirements be considered:

(a) Product requirements. Products require a variety of different environmental controls. It is important to evaluate the potential risk from the environment, and assess its potential impact on the product and its intended use.
(b) Regulatory requirements. There are regulations and guidance documents available that can serve as excellent sources of information.
(c) Standard industry practice. Information is available through conferences, seminars, websites, organizations, and communication with colleagues.

1. *Facility design, construction, and operation.* The focus for this area will be on the operation of the facility, and the ability to minimize potential contamination originating from the materials used for construction (ceiling material, paint, cabinets, shelving, flooring, etc.); the Heating, Ventilation, and Air Conditioning (HVAC) system (particulates [viable and nonviable], separation between air handling units [supply and return air], pressurization, air changes, etc.); pest control, and general building maintenance and repair.

For medical devices, the Quality System Regulation (QSR) Manual addresses contamination control under excerpt 6: Buildings and Environment. The manual reads:

> *The QS regulation requires in 820.70(e) that every manufacturer establish and maintain procedures to prevent contamination of product or equipment. These process specifications are established by the manufacturer to ensure that finished devices will meet the company's quality claims. Typical device examples are: in vitro devices that are not contaminated with microbes, detergents or rodenticides; circuits that are not contaminated with flux; implants that are not contaminated with body oils and certain implants that are not contaminated with pyrogens. Pyrogens are substances that cause fever in humans, and they arise primarily from cellular debris of gram-negative bacteria. Certain implants such as orthopedic implants are not required or expected to be pyrogen free. Other devices are required to be nonpyrogenic including: transfusion and infusion assemblies, devices that come in contact with circulating blood or cerebrospinal fluid, intraocular lenses and the surgical instruments used in their implantation, and any device labeled as "nonpyrogenic." Manufacturers should carefully control the environment in which such devices are manufactured and processed to minimize contamination with bacteria or establish a procedure for cleaning the devices.*

For drug products, 21 CFR Part 211 Subpart C addresses buildings and facilities. Section 211.42 describes the required design and construction features. Specific citations include:

(a) Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations.
(b) Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mixups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination. The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination.
(c) Operations shall be performed within specifically defined areas of adequate size. There

shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mixups during the course of the following procedures:

(1) Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging.
(2) Holding rejected components, drug product containers, closures, and labeling before disposition.
(3) Storage of released components, drug product containers, closures, and labeling.
(4) Storage of in-process materials.
(5) Manufacturing and processing operations.
(6) Packaging and labeling operations.
(7) Quarantine storage before release of drug products.
(8) Storage of drug products after release.
(9) Control and laboratory operations.
(10) Aseptic processing, which includes as appropriate.
(i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable.
(ii) Temperature and humidity controls.
(iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar.
(iv) A system for monitoring environmental conditions.
(v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions.
(vi) A system for maintaining any equipment used to control the aseptic conditions.

(d) Operations relating to the manufacture, processing, and packing of penicillin shall be performed in facilities separate from those used for other drug products for human use.

One of the first steps in the evaluation and assessment of the potential impact of the facility on the environment is to document the facility design criteria. One method is to prepare a table, such as the following:

Facility Design Criteria

Room Number	Area	Activities	Adjacencies	Proposed Classification[1]	Pressurization[2] Relative to Adjacent Hallway (Or Area)	Comments Concerns

Instructions for completing the table:

1. Enter the room number for each specific room or area.
2. Enter a brief description or the name of the room or area.
3. Briefly describe the activities or operations that take place in that area. Ensure that the list of activities is complete.
4. List the rooms or areas that are adjacent to the room or area.
5. Indicate the proposed classification for the area.
6. Indicate the pressurization differential between the specific room or area, and the adjacent rooms or areas.
7. Indicate any special concerns or challenges regarding the room, operations, classification, or adjacencies.

Once the areas are identified, and the required classifications for each area have been determined, an evaluation can be performed on the physical requirements for each area. A table similar to the following example can be used in the evaluation.

Table References

1. The classification referenced in this column relates to nonviable particulates only, and is used to refer to "relative cleaniness." It is not intended to set a standard for humidity, temperature, number of High Efficency Particulate Air (HEPA) (filters), air changes, etc.
2. Pressurization is either positive or negative, and a minimum of 0.05 inches of water at "+," 0.10 inches if water for "++."

Facility Design Considerations[3]

	Class 10,000	Class 100,000	Microbiologically Controlled/ Unclassified	Uncontrolled/ Unclassified
Ceiling	Epoxy coated or plastic polyester coated drywall; smooth, easy to clean, and resistant to cleaning agents. Solid ceiling recommended. If paneling is used, panels must be gasketed and sealed.	Cleanable tiles (or solid ceiling) are recommended. Non-shedding material.	Not required	Not required
Walls	Plastic, epoxy coated drywall or paneling; smooth, easy to clean, resistant to cleaning agents.	Same	Same	Not required
Floors	Coved, seamless, sealed to wall.	Easy to clean, sealed coving.	Same	Not required
Windows	Required for monitoring, flush, no ledges (unless slanted).	Same	Not required	Not required
Doors	Doorframes and jams must be sealed, sweeps in place, self-closing.	Same	Same	Not required
General	No protrusions, ledges, exposed piping allowed.	Same	Not required	Not required
	Access doors in walls and ceilings limited.	Same	Not required	Not required
	No drains.	Same	If present, must have break or backflow preventer; connection between process and waste drains must be avoided.	Not required
Benches, work surfaces, shelving	Cleanable, non-shedding, resistant to cleaning agents and chemicals. No wood.	Cleanable, non-shedding, resistant to cleaning agents and chemicals. Wood is not recommended. If used, it must be sealed.	Not required	Not required
Gowning	Hair net, lab coat, shoe covers, facial hair covering, and gloves.	Same. In areas where there is no potential for product exposure, gloves are not required.	Same; however, no gloves.	Not required

Table References

3. "Sterile Manufacturing Facilities." ISPE Baseline Pharmaceutical Engineering Guides for New and Renovated Facilities. Vol. 3. January 1999.
D. Vincent. "Validating and Establishing a Routine Environmental Monitoring Program." Journal of Validation Technology. *Vol. 4 No. 2. February 1998.*

Additional steps in the evaluation include the preparation of a list of observations made from a facility "walk about." A detailed list of items of concern that may have a potential impact on the environment is a useful tool in achieving an adequate level of control. Some items of particular concern include obvious dirt and dust, peeling paint, gaps under exterior doors, gaps in the ceiling tiles, and open exterior windows/doors. The mechanical systems must also be verified to "as-built" conditions. It is difficult, if not impossible, to determine how the environmental conditions can be improved if the mechanical systems are not verified as being accurate.

Prepare and carefully review product, personnel, equipment, and waste flows. Evaluate the flows in light of the potential for mix-up and contamination with regard to the desired area activities, classifications, adjacencies, pressure differentials, and special concerns.

Identify the potential risks and prioritize activities for improvement.

2. *Utilities.* The emphasis in this area will be on the operation of the utility systems, such as water, air, vacuum, and gases. There will be a heavy focus on the water system, since water is considered a critical ingredient for product.

Utilities, such as purified water and Water-For-Injection (WFI), compressed air, nitrogen, and other process gases are considered raw materials or starting materials by most regulated companies. It is likely that these materials will have direct product contact. The quality of these materials is every bit as critical to the products quality as a key chemical or ingredient. The utilities also serve as support systems to ensure equipment and processes are adequately controlled to provide reliable and reproducible products. Key support systems include electrical services, potable water, vacuum, heating and cooling systems, and plant steam. These process support systems generally do not have direct product contact; however, they may have a significant effect on the product's quality.

Utility systems must be validated and routinely monitored to ensure they are capable of providing the required quality of material or service. Monitoring may require routine sampling and testing of the resulting water, air, gas, etc. The systems must be well-maintained to ensure reproducible and reliable operation. Whether the maintenance is performed in-house or by a contract organization, well-documented procedures must be in place, and the frequency of required maintenance must be performed according to established schedules. Where recognized standards exist, those standards should be applied.

3. *Cleaning*. The focus for this area will be general facility cleaning, whether provided by external personnel or by internal personnel, equipment cleaning, preparation and storage of cleaning solutions, maintenance of cleaning equipment, such as mops, buck, etc., and procedures used for cleaning.

For new companies, review the regulatory requirements for establishing a cleaning program. Discuss personnel qualifications, written procedures, selection of cleaning agents, and recordkeeping.

Review the facility cleaning procedures used by in-house personnel, as well as procedures utilized by contract services. Review records and contracts that are in place with the contract services to ensure that adequate records are being kept and the contract is being followed. Determine if the procedures are being followed, and if they specify the cleaning agents and the preparation of those cleaning agents. Ensure that the cleaning agents, their concentration, and the procedure for use are consistent with those that have been used in the cleaning validation.

Review the written procedures for equipment cleaning. Ensure that the purpose of the cleaning is consistent with the agent chosen for use. For example, if the objective of the cleaning is to sanitize a piece of equipment, ensure that the cleaning agent chosen is designed to accomplish the desired sanitization by reviewing the technical literature available from the supplier. There is an excellent article discussing the selection of disinfectants written by Vivian Denny, et al. that appeared in the PDA *Journal of Pharmaceutical Science & Technology* entitled "Elements for a Successful Disinfection Program in the Pharmaceutical Environment" (Vol. 53, No. 3. May/June 1999). Additional reference articles on cleaning appear in the **Institute of Validation Technology** (**IVT**) *Cleaning Validation: An Exclusive Publication* featuring articles from William Hall and other cleaning experts.

Cleaning agents must be selected based on the nature of the material to be removed, extent of cleaning and/or disinfection required (i.e., is the objective of the cleaning to reduce the quantity of the material present or to sanitize the item being cleaned?), chemical and physical properties of the residues to be cleaned, surface and materials of construction of the item to be cleaned, and potential hazards to the users.

For an ideal disinfectant, the cleaning agent should be nonspecific in microbial action, nontoxic, odorless, harmless to tissue, noncorrosive to surfaces, inexpensive, and not inactivated by organic material.

During selection of cleaning agents, one must consider what organisms are potentially present and at what level. Other considerations include whether odor or fumes may affect the process, and whether the cleaning agent may adversely affect the materials to be cleaned.

To evaluate the categories of cleaning valida-

Cleaning Agent	Material (of the Item to be Cleaned)	Material (to be Removed)	Purpose of the Cleaning Step	Cleaning Procedure

tions required, a matrix approach is recommended.

Using the table, items that need to be cleaned can be grouped according to similarities. Once the groups have been identified, determine which items are the most difficult-to-clean within each group by observing the cleaning process, discussing cleaning with individuals responsible for the cleaning, and evaluating the potential for inadequate cleaning. Focus the validation efforts on those items determined to be the most challenging to clean. This approach has been shown to be practical and effective.

Documented cleaning procedures should include the specific agent validated for use, its expiration date, precautions during handling, instructions for preparation, set or contact time required, and whether there is a rinse required. The procedure must also specify the quality of water to be used to prepare the cleaning solution. It is recommended that purified water at a minimum be used for preparing cleaning solutions.

Personnel assigned to cleaning must be adequately trained in written cleaning procedures, requirements for gowning, if required, and record-keeping. Once personnel have been trained, effectiveness checks should be conducted to confirm the training. Records should be monitored frequently to ensure they are accurate and complete.

4. *Raw* materials and components. The emphasis in this section will be on those raw materials and components that are likely (or somewhat likely) to contribute bioburden to product. This material category includes both product ingredients, as well as items that have direct product contact, such as cleaning and sanitizing agents.

It is common for both diagnostic and pharmaceutical companies to utilize a wide variety of materials that may not be fully characterized or well-defined. A material may have:

- Inherent variability as a result of its starting materials or the process parameters.
- Biological origin.
- Bioburden associated with either its starting materials or its processing.

As a result of the potential impact on finished products, the raw materials that may have an effect on products as a result of bioload, must be identified. These materials must be carefully evaluated and controlled. This may require the addition of added controls on the supplier to maintain and deliver these selected materials within established specifications for bioburden or sterility. Special packaging, handling, sampling, and storage may be required to maintain the material's integrity.

According to 21 Code of Federal Regulations (CFR) 211.84:

> *"Testing and approval or rejection of components, drug product containers, and closures. (d)(5). Each lot of component, drug product container, or closure that is liable to contamination with filth, insect infestation, or other extraneous adulteration shall be examined against established specifications for such contamination. (b)(6). Each lot of component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use."*

According to 21 CFR 211.113:

> *Control of microbiological contamination. (a) Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed. (b) Appropriate written procedures, designed to prevent microbiological contamination of drug products purported to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process.*

5. *Personnel.* The focus in this area is personnel hygiene. There are seven (7) elements that affect personnel hygiene in an environmentally controlled facility.

(a) Separation of activities. There are different requirements for each zone or separate area, including control of access, personnel flow, and protection of the cleanest area from those areas less clean.

(b) Gowning. Clothing must be appropriate for the product, and be based on relative risk. Personnel training in proper gowning technique must be provided.
(c) Cleaning and disinfection. There must be a comprehensive plan for the complete facility. The plan must be written, documented, and effective.
(d) Training. Personnel training must be performed, documented, and effective. Training should include basic principles of microbiology, aseptic technique, cleanroom classification, validation, potential contamination sources, contamination controls, quality systems, and cGMPs.[4] The depth of training in each of these areas should be dependent on the assignments and responsibilities of the individuals being trained.

Training can be performed using in-house personnel, consultants, videos, publications, outside seminars and workshops, or using software-based training. Software-based programs are gaining popularity and have been shown to provide very effective training. One company offering "e-based" training is Eduneering (www.Eduneering.com). Eduneering offers a wide variety of courses applicable to regulated companies. As Bill Hall (Hall and Associates) described:

> *"..the Internet poses a wonderful opportunity to take the training to the company rather than always have to take the individual to the training. The new technology of the Internet gives us the technical mechanism to do just that. It also allows the individual to stay at work and still train at their convenience. So the advantages are that it can be done at the work site and at the convenience of the individual. It eliminates the travel expense."*

Regardless of the method used to deliver training, the training program must include the following:

■ Training Plan. This includes a plan for each new employee, as well as a renewal plan for existing employees. The plan and a schedule for retraining should be reviewed with the employee at each evaluation interval.

■ GMP training. This training should be performed at least once yearly. In the event there are audit findings that warrant focused training, special sessions should be conducted to address identified weak areas.

■ Job specific training. On-the-job training should be performed by having the employee first observe, then perform the work under close supervision until the trainer determines that the trainee can perform the work independently.

■ Safety training. All employees should be trained in applicable safety requirements prior to work assignments that may pose a potential risk to themselves or others.

■ Training on procedures. This training should be performed as new procedures are introduced, and as existing procedures are revised.

(e) Motivation. Personnel have a significant impact on the cleanliness of the environment in which they work. They must be motivated to adhere to established procedures, communicate with others, perform self-inspections, and be continually aware of the potential impact they may have on the environment.
(f) Written procedures. The procedures must be easy-to-follow, clearly written, accessible, and complete in order to ensure that the procedure will be performed reproducibly, and to the same standard each time.
(g) Monitoring. Monitoring must be used to confirm that required parameters are and remain within established limits. The limits should be based on the relative risk to the product. The techniques used for monitoring should provide meaningful results.

6. *Waste flow.* The focus for this area will be the flow of waste from its origin to the staging area, and from the staging area to the waste pickup location. The collection site, method of transporting from the collection site, container used for the transport, pathway taken to reach the staging location, etc. must be reviewed for potential impact on the product.

Environmental regulations may have a significant impact on the waste water systems designed and implemented for individual products. Wastewater may require neutralization, inactivation, etc. prior to release to the drain.

Spill procedures must be established based on the potential risk of the spill, and the adjacent areas that may be impacted by the spill. Spill drills should be performed to ensure that the procedures for handling spills of significant size can be effectively handled. Safety equipment should also be

strategically located in the areas of highest probability for a spill. Personnel should be trained in the spill procedures.

The flow of waste through the facility may have a potential impact on the environment, and must be carefully evaluated. Totes, carriers, carts, or other means of containment are commonly used for transporting waste. Waste transport can be scheduled before or after production. A passthrough may be used for transitioning waste from one area to another.

Ensure that the areas for holding waste are appropriate for the waste being held. The containers used must be adequate in size and number to prevent overfilling. Access to the waste holding areas should be limited to authorized personnel only. The hold time should be as short as possible to avoid unnecessary buildup prior to pickup or disposition.

7. *Preservative systems*. The focus for this section will be on the selection of the preservative, its concentration, and the formulation in which it is used. Preservative Effectiveness Testing (PET) must be conducted on groups of products with identical or nearly identical formulations. In addition to PET, an environmental challenge study should also be conducted. This second study is a challenge of environmentally isolated organisms spiked into the product. The product is then evaluated over time for both microbial growth, as well as actual product performance.

The object of preserving product is to ensure that the product is both safe and stable. Studies must be conducted to determine the effective concentration to preserve the product during processing, storage, and use by the customer.

Microorganisms are unique and have a wide variety of metabolic capabilities. There are microbes that can be grown essentially everywhere, and can utilize any organic and some inorganic compounds as substrates for growth. Do not make any assumptions when selecting a preservative system.

The choice of a preservative must be based on the formulation of the product and the physiochemical characteristics of the preservative. There are known incompatibilities that will have a significant impact on the effectiveness of the chosen preservative. According to the Guide to Microbiological Control in Pharmaceuticals,[5] the ideal preservative should have the following characteristics:

(a) Broad spectrum of activity.
(b) Effective and stable over a broad range of pH.
(c) Compatible with the formulation and packaging material.
(d) Does not affect the physical properties of the product (i.e., color, clarity, odor, flavor, viscosity, texture).
(e) Suitable oil-to-water ratio to ensure effective concentration in the aqueous phase.
(f) Inactivate microorganisms rapidly to prevent microbial adaptation.
(g) Safe.
(h) Compliant with regulatory requirements.
(i) Cost effective.

The optimum preservative must be chosen based on all of these factors. Testing must demonstrate and document the selection, stability, and effectiveness of the product, as well as the preservative.

8. *Environmental Monitoring*. The focus here is to monitor the success and adequacy of the program. Monitoring must be done at frequent intervals. The frequency of sampling should be based on the product requirements. The testing must include both viable and nonviable particulate monitoring. Action and alert levels should be established that are consistent with the data generated, as well as the product requirements.

According to FDA's Medical Device Quality Systems Manual,[6] an appropriate system for regular monitoring should be established and maintained for each of these factors to be controlled for a given operation. This will ensure that equipment is performing properly, and that the quality of the environment is within specifications. When a particle count Class is specified, monitoring of airborne particulates is usually done with an air sampler. Monitoring of work surfaces for microbes (colony forming units) may be done with surface contact plates or settling plates. However, settling plates should not be used for monitoring when horizontal laminar air flow is used. They are ineffective for this type of flow.

All sampling should be done per written procedure and the data recorded. Further, periodic inspections of environmental controls and documentation of the inspections are required by the QS regulation. The inspection checkoff form or other record should be kept simple.

An evaluation of the HVAC system is necessary to determine how the system was designed, is cur-

rently operating, and what quality of air it is capable of delivering. Once the system is known and understood, then an evaluation of the cleaning procedures can be performed. Unless the cleaning program is reliable and reproducible, the EM program cannot be effective.

In addition to HVAC and cleaning procedures, gowning and personnel training should be reviewed for potential weakness or opportunities for improvement. A gap analysis should be performed and corrections made. Once the support systems are in place, the EM program can be implemented.

The EM program is comprised of the following elements:

(a) Sampling plan (sampling locations and justification for selection of the locations).
(b) Schedule for frequency.
(c) Equipment and validation.
(d) Supplies.
(e) Microbiology laboratory.
(f) Test methods and method validation.
(g) Data collection and trending tools.
(h) Alert and action levels.
(i) Investigations and corrective actions.
(j) Effectiveness checks.
(k) Recordkeeping and reporting requirements.

There are several excellent resources published on environmental monitoring. The most recent is the Technical Report No. 13 (Revised) from the Parenteral Drug Association (PDA) entitled *Fundamentals of an Environmental Monitoring Program*. Another was published by the **Institute of Validation Technology** in February, 1998 entitled *Technical Guide: Validating and Establishing a Routine Environmental Monitoring* by David Vincent.[7]

Conclusion

An ECP must be supported with control systems, and carefully balanced with facility design, cleaning procedures, personnel, flow patterns, and environmental monitoring. The program must be developed based on product requirements, existing environmental constraints, and what can "practically" be performed, managed, and controlled on a routine basis. Use logic. Understand the underlying rationale behind the program, and the relative risks associated with each element that supports the program. Focus on the objectives of the program, and ensure adequate control is in place to meet those objectives.

There is no substitute for a common-sense approach to the design and implementation of an ECP. ❑

From FDA's Medical Device Quality Systems Manual

Any practices or factors from the following list that the manufacturer has deemed appropriate and elected to use should be specified and routinely performed or followed. Some additional factors that should be considered when planning and using a controlled environment include:

- Proper attire and dressing anteroom
- Controlled use of, and entry into, controlled areas
- Prohibiting eating, drinking, smoking, or gum chewing
- Preventing use of lead pencils
- Regulating the storage of glassware and containers
- Preventing or controlling the cutting, tearing or storage of cardboard, debris, etc.
- Cleaning the room and production equipment per written procedure
- The original design and cleaning of work surfaces and chairs
- Selecting correct furniture and eliminating all nonessential equipment
- Controlling room air quality (amount of particulates, pressure, velocity, and exchange rate)
- Eliminating electrostatic charges by controlling work surface composition or grounding
- Ensuring cleanliness of raw materials, components and tools
- Controlling the purity, sterility, and nonpyrogenicity of process water and maintaining prefilters, HEPA filters, and electrostatic precipitators

References

1. The classification referenced in this column relates to nonviable particulates only, and is used to refer to "relative cleanliness." It is not intended to set a standard for humidity, temperature, number of HEPAs, air changes, etc.
2. Pressurization is either positive or negative, and a minimum of 0.05 inches of water at "+," 0.10 inches of water for "++."
3. ISPE. "Baseline Pharmaceutical Engineering Guides for New and Renovated Facilities." Vol. 3. Sterile Manufacturing Facilities. January, 1999.
4. Technical Report No. 35: A Proposed Training Model for the Microbiological Function in the Pharmaceutical Industry. Vol. 55, No. 6. November/December 2001.
5. Editors S. Denyer and R. Baird. "Guide to Microbiological Control in Pharmaceuticals." Ellis Horwood. 1990. Pps 246-247.
6. FDA's Medical Device Quality Systems Manual: A Small Entity Compliance Guide. December, 1996.
7. D. Vincent. "Validating and Establishing a Routine Environmental Monitoring Program." *Journal of Validation Technology*. Vol. 4 No. 2. February, 1998.

Suggested Reading

1. J. Agalloco. "Qualification and Validation of Environmental Control Systems." *Journal of Parenteral Science and Technology*. Vol. 50, No. 5 (1996).
2. V. F. Denny, E.M. Kopis, F.J. Marsik. "Elements For a Successful Disinfection Program in The Pharmaceutical Environment." *Journal of Parenteral Science and Technology*. Vol. 53, No. 3 (1999).
3. Technical Report No. 35. "A Proposed Training Model for the Microbiological Function in the Pharmaceutical Industry." *Journal of Parenteral Science and Technology*. Vol. 55, No. 6 (2001).
4. J. Akers and J. Agallaco. "Environmental Monitoring: Myths and Misapplications." *Journal of Parenteral Science and Technology*. Vol. 55, No. 3 (2001).
5. J. Wilson. "Environmental Monitoring: Misconceptions and Misapplications." *Journal of Parenteral Science and Technology*. Vol. 55, No. 3 (2001).
6. Technical Report No. 13 (Revised). "Fundamentals of an Environmental Monitoring Program." *Journal of Parenteral Science and Technology*. Vol. 55, No. 5 (2001).
7. Convention for the Mutual Recognition of Inspection in Respect to the Manufacture of Pharmaceutical Products. "Contamination Risks in the Manufacture of Parenterals." Seminar held in Baden on September 13-15, 1989.
8. S.P. Denyer and R.M. Baird. "Guide to Microbiological Control in Pharmaceuticals." Ellis Horwood Publisher, 1990.
9. D. W. Vincent. "Validating and Establishing a Routine Environmental Monitoring Program for Clean Room Environments." *Journal of Validation Technology*. Vol. 4, No. 2 (1998).
10. Baseline Pharmaceutical Engineering Guide. "Pharmaceutical Engineering Guides for New and Renovated Facilities." Sterile Manufacturing Facilities. Vol. 3.1999.
11. Baseline Pharmaceutical Engineering Guide Series. "Introduction to Biotech." ISPE Conference. June 5-6, 2000.
12. FDA's Medical Device Quality Systems Manual: A Small Entity Compliance Guide. December 1996.
13. Technical Report No. 33. "Evaluation, Validation, and Implementation of New Microbiological Testing Methods." *Journal of Parenteral Science and Technology*. Vol. 54, No. 3 (2000).
14. International Standard ISO 14644-1. "Cleanrooms and associated controlled environments-Part 1: Classification of air cleanliness." 1999.
15. International Standard ISO 14644-2. "Cleanrooms and associated controlled environments-Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1." 2000.
16. International Standard ISO 14644-4. "Cleanrooms and associated controlled environments-Part 4: Design, construction and start up." 2001.

Environmental Control Program Standard Operating Procedures

1. Environmental Controls
2. Water Monitoring and Trending
3. Viable Air Monitoring and Trending
4. Nonviable Air Monitoring and Trending
5. Surface Monitoring and Trending
6. Personnel Monitoring and Trending
7. Personnel Training and Qualification
8. Facility Cleaning Procedures
9. Equipment Cleaning Procedures
10. Product Bioburden Testing and Trending
11. Personnel Flow
12. Waste Flow
13. Personnel Hygiene
14. Gowning
15. Facility Change Control
16. Mechanical Rounds
17. Environmental Failures and Investigation