Infrastructure: Facilities, Utilities, and Equipment Cleaning and Sanitization

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Welcome to “ASQ CPGP Basics.”

This feature discusses various good manufacturing practice (GMP) topics from the American Society for Quality (ASQ) Body of Knowledge for the Certified Pharmaceutical GMP Professional (CPGP) program. We intend this column to provide basic theory and application of GMP topics useful to quality professionals. The key objective for this column: Useful information.

The American Society for Quality adopted its 15th certification, the ASQ Certified Pharmaceutical GMP Professional (CPGP), on May 1, 2008. This is a sector-specific program that develops in-depth GMP knowledge of a professional serving the pharmaceutical or allied industries anywhere in the world. The Journal of GXP Compliance will publish excerpts of CPGP handbook chapters provided by handbook contributing authors as well as other CPGP-related articles. For complete information on the CPGP exam and its contents, please refer to the ASQ website at asq.org/certification/pharmaceutical-gmp/index.html.

The ASQ CPGP Body of Knowledge is a comprehensive compilation of GMP principles comprising US and international compliance requirements. It addresses elements associated with human and veterinary drugs and biologics, ectoparasitacides, dietary supplements, active drugs, excipients, packaging, and labeling.

Specific major sections of the Body of Knowledge include regulations; quality systems; laboratory systems; infrastructure such as equipment, facilities, and utilities; materials and supply chain; sterile and non-sterile manufacturing; filling, packaging, and labeling; and product development and technology transfer. This subject matter describes a broad and expansive breadth of information. Each of these sections may comprise specific and distinct technology and language. Technical principles may be unique and esoteric in specific areas. We intend to discuss these topics in a clear and meaningful way so that our readers in different compliance areas within the organization will be able to understand and apply the principles discussed.

Reader comments, questions, and suggestions are requested. Suggestions for future discussion topics from the ASQ Body of Knowledge to be addressed
KEY POINTS
The following key points are discussed:
• Facilities, utilities, and equipment cleaning and sanitization are vital topics in the American Society for Quality (ASQ) Certified Pharmaceutical GMP Professional (CPGP) program.
• Equipment cleaning and associated facilities are clearly addressed in US Food and Drug Administration good manufacturing practice (GMP) regulations and European Union (EU) guidelines.
• Cleaning processes must be proceduralized and performance documented. Cleaning of multi-product equipment must be validated.
• Removal of residual cleaning agent or sanitizer must also be validated.
• Use of rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents must also be proceduralized. Their use must not contaminate product, equipment, closures, and related materials.
• The FDA GMP Guidance on Sterile Drug Products Produced by Aseptic Processing and US Environmental Protection Agency (EPA) also address disinfectants and the need to monitor organism susceptibility.
• EU Annex 1 addresses use and storage of disinfectants. Unless the site has created and validated a production-like aseptic sterilizing filtration process and validated the sterility through expiration date, European Medicines Agency expects monitoring of the solution over its shelf-life.
• The efficacy of commonly used sanitizers is reported.
• Pest control programs require QA oversight including use of suitable rodenticides, insecticides, fungicides, or fumigating agents. A system must exist for the continual capture for identification and analysis of crawling and flying pests by a pest control expert. A system should also exist for the reporting and recording of pest sightings by any personnel.
• GMP compliance professionals must be well versed in the above topics to assure that their areas of responsibility meet regulatory requirements. They should be focused on high-risk areas. Non-aseptic areas perceived to be of lesser risk should also be appropriately controlled. A well-designed environmental monitoring program with appropriate data review is invaluable in maintaining facility standards.
• A glossary of terms associated with facilities, utilities, and equipment cleaning, sterilization, and sanitization is provided.

INTRODUCTION
This first issue of “ASQ CPGP Basics” addresses the cleaning and sanitization of facilities, utilities, and equipment. This is a vital topic in the Certified Pharmaceutical GMP Professional (CPGP) program. Cleaning activities associated with facilities, utilities, and equipment infrastructure is a fundamental responsibility for all good manufacturing practice (GMP) professionals. Because this topic is often taken for granted and is not directly included in manufacturing batch records, problems may not be highlighted in the same way as those affecting product “out the door.”

When problems are discovered with infrastructure cleaning and sanitization, they may have major impact on operations. These problems may require significant effort and cost to correct. More importantly, they may affect literally every product manufactured during the time period of the problem. The control of infrastructure is fundamental to GMP operations.
ASQ CERTIFIED GMP PROFESSIONAL BODY OF KNOWLEDGE

SECTION IV.F. CLEANING, SANITIZATION, AND STERILIZATION SYSTEMS

1. Washing Facilities
   Verify that washing facilities are adequate and properly located.

2. Cleaning Procedures
   Review cleaning procedures in accordance with prior cleaning validation, whenever validation is required and performed.

3. Sanitization Procedures
   Review sanitization procedures for facilities and equipment, including details on cleaning schedules, methods, equipment, materials, etc., and verify that sanitizers, disinfectants, sporicides, and sterilants are used in accordance with marketing authorization and any required validation studies.

4. Pest Control
   Review and verify that a pest control program is in place and that it uses authorized rodenticides, insecticides, fungicides, fumigating agents, and appropriate traps for pest elimination, etc.

CLEANING AND SANITIZATION

The following systems are addressed in the ASQ CPGP Body of Knowledge:

- **Washing facilities.** Verify that washing facilities are adequate and properly located.
- **Cleaning procedures.** Review cleaning procedures in accordance with prior cleaning validation, whenever validation is required and performed.
- **Sanitization procedures.** Review sanitization procedures for facilities and equipment, including details on cleaning schedules, methods, equipment, materials, etc., and verify that sanitizers, disinfectant, sporicides, and sterilants are used in accordance with marketing authorization and any required validation studies.
- **Pest control.** Review and verify that a pest control program is in place and that it uses authorized rodenticides, insecticides, fungicides, fumigating agents, and appropriate traps for pest elimination, etc.

Washing Facilities And Cleaning Procedures

“Washing and cleaning equipment should be chosen and used in order not to be a source of contamination” (1).

This statement is a fundamental starting point for any discussion of GMP equipment and parts cleaning. Sponges and mops used in grades A or B areas must be of material and design to minimize shedding of particles. Large and small GMP equipment and parts amenable to clean-out-of-place (COP) must have facilities or suites equipped with the necessary utilities (e.g., water meeting World Health Organization drinking water standards, purified water, and possibly water for injection [WFI]). Take-offs or hoses from the purified water and WFI loops must have mechanisms (e.g., backflow preventers and check valves) or procedures that prevent back-siphonage of cleaning solutions and detergents. Flow of equipment or cleaning facility layout must preclude dirty equipment and parts from contaminating or mixing with clean equipment and parts. Annex 1 of European Union (EU) GMP guidelines section on “Premises” prohibits sinks and drains from grade A and B areas. Therefore, equipment and parts cleaning may not occur in these aseptic core suites. If equipment and parts cleaning suites exist within grades C or D areas, any floor drains “should be fitted with traps or water seals to prevent back-flow.” Also, sink drains, glassware, equipment washer drains, and autoclave drains must have air breaks “between the machine or sink and the drains” (1).

Regulation 21CFR 211.67, “Equipment Cleaning and Maintenance” (2) states,

(a) Equipment and utensils shall be cleaned, maintained, and sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

(b) Written procedures shall be established and followed...

(c) Records shall be kept of maintenance, cleaning, sanitizing, and inspection…
GMP equipment and parts cleaning must be proceduralized to ensure consistency over time and operator-to-operator. If equipment or parts are prone to accumulation of active pharmaceutical ingredient (API) or are to be exposed to multiple products or materials, then cleaning procedures must be validated. If the equipment, part, utensil, or labware has product exposure or sensitive quality control assay exposure, then a cleaning procedure using detergent or chemical besides water must be validated for removal of detergent or chemical residue. Also, a sanitizer that leaves a residue on a product contact equipment or part must be followed by an appropriate rinsing or removal agent and validated process that ensures no sanitizer residue. Note: In the absence of cleaning or rinse validation, 100% cycle verification of residue removal is permitted using a validated analytical and/or microbiological assay and test.

**SANITIZATION PROCEDURES**

Sanitization procedures are addressed in 21CFR 211.56, which states:

There shall be written procedures for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents. Such written procedures shall be designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, or drug products and shall be followed. Rodenticides, insecticides, and fungicides shall not be used unless registered and used in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (7U.S.C. 135) [= FIFRA].

United States Pharmacopeia (USP) informational general chapter <1072>, “Disinfectants and Antiseptics,” states:

A sound cleaning and sanitization program is needed for controlled environments used in the manufacture of Pharmacopeial articles to prevent the microbial contamination of these articles. … When disinfectants are used in a manufacturing environment, care should be taken to prevent the drug product from becoming contaminated with chemical disinfectants as a result of the inherent toxicity of the disinfectants. … The development of microbial resistance to antibiotics is a well-described phenomenon. The development of microbial resistance to disinfectants is less likely, as disinfectants are more powerful biocidal agents than antibiotics and are applied in high concentrations against low populations of microbes usually not growing actively, so the selective pressure for the development of resistance is less profound. However, the most frequently isolated microbes from an environmental monitoring program may be periodically subjected to use dilution testing with the agents used in the disinfection program to confirm their susceptibility. … It is prudent to augment the daily use of bactericidal disinfectant with weekly (or monthly) use of a sporicidal agent. The daily application of sporicidal agents is not generally favored because of their tendency to corrode equipment and because of the potential safety issues with chronic operator exposure.

The FDA Guidance on Sterile Drug Products Produced by Aseptic Processing, Section X. A. 3 and 4, states:

The suitability, efficacy, and limitations of disinfecting agents and procedures should be assessed. The effectiveness of these disinfectants and procedures should be measured by their ability to ensure that potential contaminants are adequately removed from surfaces. To prevent introduction of contamination, disinfectants should be sterile, appropriately handled in suitable (e.g., sterile) containers and used for no longer than the predefined period specified by written procedures. … a sound disinfectant program also includes a sporicidal agent, used according to a written schedule and when environmental data suggest the presence of spore-forming organisms.

The US Environmental Protection Agency (EPA) licenses chemicals whose manufacturers claim efficacy to disinfect inanimate objects. EPA evaluates disinfectant efficacy chiefly via either of two methods originated by the Association of Official Analytical Chemists (AOAC), as follows:
• **Use/Dilution Method.** An organism is dried to a rod made of glass, stainless steel, polished porcelain, or other non-reactive material. The rod is then submerged for 10 minutes or other claim time in a container with the disinfectant being tested (without touching side of container). The rod is then raised and allowed to drain. A RODAC plate with agar and the appropriate nutrient is placed on the rod to remove organisms for testing and incubated a set time. Zero growth permits disinfectant to pass test.

• **Spray Method (also called the Hard Surface Carrier Test).** An organism is dried to a measured surface area of a specific material. The disinfectant product is sprayed according to manufacturer directions. The surface is left until sufficient contact time according to directions. The surface is scraped and applied to a RODAC plate of appropriate media then incubated a set time. 0 cfu means Pass.

Annex 1 of the EU guidelines (1), section titled “Sanitization” (paragraph 62) states the following about disinfectants used inside grade A or B cleanrooms:

Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilized. Disinfectants and detergents used in Grades A and B areas should be sterile prior to use.

Regarding the EU requirement for monitoring of disinfectants prepared at ready-to-use (RTU) dilution and in its final applicator bottle, the following may be concluded: Unless the site has created and validated a production-like aseptic sterilizing filtration process and validated the sterility through expiration date along with validating the container closure of the application container, the full expectation by the European Medicines Agency (EMA) is for “monitoring” of the solution over its shelf-life. Alternatively, the supplier of pre-filled, pre-sterilized (aseptic filtered or terminally sterilized) must have had its validation data audited by the drug manufacturer, including container closure validation. This also holds true for liquid, gel-like, and moist pad antiseptics used in the sterile core. The latter, due to their exposure (sheets are pulled like tissues from a container), cannot avoid the requirement for drug manufacturing site disinfectant solution “monitoring.” The alternative, onerous requirement for “monitoring” entails sampling the disinfectant solution or wipe on a media containing a validated neutralizer against the bactericidal active ingredients.

The following state the efficacy of various sanitizers (5):

- Chlorhexidine has a wide spectrum of antibacterial activity against both Gram-positive and Gram-negative vegetative bacteria.
- Quaternary ammonium compounds (QACs) have a high antimicrobial activity (vegetative cells) if its carbon chain length is C8 to C18 (if aliphatic). These compounds, being positively charged, are also surfactants (i.e., have detergent or cleaning properties to get inside crevices). Unfortunately, QACs are not mycobactericidal (e.g., against tuberculosis-causing organism) or effective against the Gram-negative bacteria *E. coli*, *P. aerugeinosa*, and *S. typhimurium*. They are more active at alkaline or neutral pH.
- Phenolics are effective against both Gram-positive and Gram-negative vegetative bacteria, but only slowly effective towards bacterial spores. They’re virucidal activity cannot be generalized (enveloped viruses more susceptible).
- Glutaraldehyde (usually supplied at 2% v/v—supplied alkaline but made acidic before use) possesses sporicidal activity (vegetative cells covered), mycobacterial, and fungal spore efficacy, and various types of viruses.
- Formaldehyde (a carcinogen) is widely bactericidal, sporicidal, virucidal, and effective against protozoa.
- Iodophors. Surface-active agents (surfactants) can solubilize iodine to form these compounds containing microbicidal activity over a wide pH range (e.g., povidone-iodine solution of 10% w/v). These are sporicidal.
• Chlorine-releasing compounds. The most common are hypochlorites and N-chloro compounds. They are irritant and corrosive but with high antimicrobial activity, including sporidical. A bit low in mycobacterial activity, they are also active against lipid and non-lipid viruses. NaOCl is more active at acid than at alkaline pH. Diluted RTU solutions have a short shelf life (must be qualified). They are virucidal.
• Chlorine dioxide is an alternative to NaOCl and retains biocidal activity over a wide pH range (note: Oxine is a sodium chlorite solution that, when acidified, generates chloride dioxide, giving a mixture of chlorite and chlorine dioxide. It is more efficacious against pathogenic bacteria than Chloride Dioxide alone). It is virucidal.
• Peroxygens (includes Hydrogen Peroxide and Peracetic Acid). H₂O₂ is used at varying strengths (35, 50, and 90%). H₂O₂ is bactericidal, sporidical. H₂O₂ can also be used as an antiseptic besides a sanitizing agent.
• Peracetic acid is available commercially as a 15% aqueous solution—35% is potentially explosive. Peracetic acid has broad spectrum of activity, including bacteria, their spores, molds, yeasts, algae, and viruses.
• Ethylene Oxide. By its alkylating properties on proteins (used at proper concentration, temperature, and relative humidity), it’s a potent sterilant and sporidical.
• Ozone (O₃) is bactericidal, virucidal, and sporicidal.
• Sodium Hydroxide is active against all microorganisms, including protozoa and prions.

PEST CONTROL
Any building used in the manufacturing, processing, packaging, or storage of pharmaceutical products must be free of infestation. The pest control program requires appropriate quality assurance (QA) oversight. Procedures shall describe the use of suitable rodenticides, insecticides, fungicides, or fumigating agents. Rodenticides, insecticides, fungicides, or fumigating agents should be of the appropriate grade, approved by local regulations, and approved via documentation by the drug manufacturing site quality unit or quality assurance. Pest control records must be generated and retained. A system must exist for the continual capture for identification and analysis of crawling and flying pests by an entomologist or pest control expert. When the latter is contracted by a manufacturing site, a quality/technical agreement must describe all the activities and responsibilities of the contract-giver and the contractor. A system should also exist for the reporting and recording of pest sightings by any personnel besides the contractor.

IMPLICATIONS FOR COMPLIANCE PROFESSIONALS
This brief introduction from the CPGP Body of Knowledge is a recommended starting point for discussion on facilities, utilities, and equipment. Cleaning, sterilization, and sanitization are basic activities associated with infrastructure. These are critical activities supporting manufacturing operations. Although cleaning, sterilization, and sanitization activities should be conducted according to risk management prin-

“DID YOU KNOW...?”
1. USP general chapters between <1000> and <1999> are technically informational non-mandatory from a regulatory standpoint. Yet FDA’s Brian Hasselbalch at an ASQ-FDA Southeast Conference several years ago stated that FDA considers these chapters “good science,” (i.e., these chapters should be relied on). Therefore, USP <1072> is in the “should” category.
2. Not all sporidical disinfectants are corrosive to stainless steel (e.g., H₂O₂ and peracetic acid). A site need not wait for a bacillus to be identified before rotating in a sporidical agent. Still too many sites argue for only ad hoc sporidical.
3. Drains with air breaks before piping at a site are as critical a preventive design as a backflow preventer on the town/city water line into a plant. These are simple and inexpensive but can save thousands in backflow damage.
4. Pest control and bacterial contamination control are both about protecting materials from organism contamination and/or digestion.
ciples, there are fundamental requirements associated with these activities. Compliance professionals must be well versed in these topics and assure that their areas of responsibility meet regulatory requirements. Close working relationships with site microbiologists are highly recommended as needed. Aseptic manufacturing areas are often well-controlled regarding these considerations. Non-aseptic areas perceived to be of lesser risk may not be adequately controlled. Compliance professionals should be wary of overlooked details and procedures that have been compromised in favor of cost savings, headcount reductions, or other economic benefit. A comprehensive environmental monitoring program is invaluable in maintaining facility standards. This program should be appropriate for risk involved. Monitoring data must be appropriately and routinely reviewed and analyzed. Infrastructure cleaning, sanitization, and sterilization are vital to manufacturing and must be treated as critical to successful daily operations.

REFERENCES
2. FDA, 21CFR 211, Title 21—Food And Drugs Chapter I—Food And Drug Administration Department Of Health And Human Services, Subchapter C—Drugs: General Part 211, Current Good Manufacturing Practice For Finished Pharmaceuticals, 43 Federal Register 45077, Sept. 29, 1978.

GLOSSARY
Antisepsis: the act or process of chemically reducing viable organisms on living tissue, including skin oral cavities and open wounds.
Bioburden: the total quantity of recoverable microbes present on a defined surface, surface area, or within a solid or liquid material.
Cleaning: the physical removal of soil, organic debris, and particulate from surfaces.

Cleaning validation: documented evidence with a high degree of assurance that a cleaning process will consistently yield product contact surfaces that meet pre-determined acceptance criteria and critical quality attributes (visual and residual levels).
Cleaning validation master plan: an overview document that describes, at a high level, the entire site’s cleaning validation strategy, structure, content, and actual plan or schedule (latter may be an attachment or a stand-alone, referenced document).
Contamination: the undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, API, finished drug, primary surface, or equipment.
Disinfection: the act or process of chemically or physically destroying or removing vegetative pathogens on inanimate objects (a disinfectant is a chemical or physical agent that assists disinfection).
Flora: the identified microbes (to species level) found at a specific time in an operating area(s), room(s), or the collection of rooms used in manufacturing, testing, and warehousing (as in the whole facility); this includes microbes isolated from primary surfaces, air, as well product, intermediates, raw materials, etc. tested and determined to be contaminated after a specific area or suite exposure.
Housekeeping: general cleaning (including sweeping) and removal of accumulated process waste, dirty equipment, utensils, and other non-product materials resulting from normal manufacturing or warehousing activities.
Microbiological contamination: the presence of one or more various bacteria, yeasts, mould, protozoa, or their toxins/by-products (e.g., endotoxins or exotoxins), that could adversely affect the product or a patient’s health and safety.
Microorganisms (or microbes): bacteria, mold, yeast, protozoa.
Mycobacterial: of or relating to Mycobacterium tuberculosis.
Pathogenic: regarding a microbe that is harmful to man or animal.
Pest control: a system for preventing, evaluating, and eliminating infestation by rodents, insects, birds, and other vermin.
Prion: an infectious agent composed of protein that can transmit its (misfolded) configuration to native, similar
proteins in an infected animal’s central nervous system, causing transmissible spongiform encephalopathy.

**Sanitization:** the act or process, physical or chemical, of reducing viable organisms on a surface to a defined acceptance level (a sanitizer is a physical or chemical agent that assists sanitization); sterilization is a subset of sanitization. Surface sanitization concerns primary surfaces and product- or raw-material-contacting durable equipment surfaces.

**Sporicide:** A chemical agent that destroys bacterial and fungal spores when used in sufficient concentration for a specified contact time. It is expected to kill all vegetative organisms. Note: Health Canada prohibits a supplier from labeling a non-sporicidal disinfectant with claims against the vegetative cells of spore-forming bacteria whose spores may be the primary means of spread of healthcare-associated infections, which could mislead users into assuming that the disinfectant has sporicidal effectiveness.

**Sterilization:** the act or process, physical or chemical, of destruction or elimination of all viable organisms (including bacterial and fungal spores, viruses, protozoa) in the inanimate environment; never being considered absolute, it is characterized by a probability of presence of one or more viable organisms and expressed as $10^{-n}$. A sterilant is an agent that can assist sterilization; sterilants are liquid or vapor-phase agents. All sterilants are sporicides, but not all sporicides are sterilants.

**ARTICLE ACRONYM LISTING**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>AOAC</td>
<td>Association of Official Analytical Chemists</td>
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<td>API</td>
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<td>ASQ</td>
<td>American Society for Quality</td>
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<td>COP</td>
<td>Clean-Out-Of-Place</td>
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<td>CPGP</td>
<td>Certified Pharmaceutical GMP Professional</td>
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<td>US Environmental Protection Agency</td>
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<td>FDA</td>
<td>US Food and Drug Administration</td>
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<td>Quality Assurance</td>
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<td>QACs</td>
<td>Quaternary Ammonium Compounds</td>
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<td>RTU</td>
<td>Ready-to-Use</td>
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<td>USP</td>
<td>United States Pharmacopeia</td>
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<td>WFI</td>
<td>Water for Injection</td>
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